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A 2-month-old boy is brought to the emergency department due to progressively worsening "floppiness" and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38-year-old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. Physical examination shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient's condition?

A. Botulism
B. Down syndrome
C. Galactosemia
D. Hirschsprung disease
E. Hypothyroidism
F. Phenylketonuria

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and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38-year-old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. Physical examination shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient's condition?

A. Botulism (20%)
B. Down syndrome (11%)
C. Galactosemia (10%)
D. Hirschsprung disease (5%)
✓ E. Hypothyroidism (41%)
F. Phenylketonuria (9%)

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Congenital hypothyroidism

Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months) ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*
Prognosis	• No deficits if treatment started in neonatal period • Untreated disease is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient)

*Avoid coadministration with soy products, iron, or calcium.

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*Avoid coadministration with soy products, iron, or calcium.

Congenital hypothyroidism is one of the most common causes of preventable intellectual disability. Most cases are due to thyroid dysgenesis (agenesis, hypoplasia, or ectopy), and iodine deficiency is a common cause in areas endemic for iodine deficiency (eg, Europe).

Neonates initially have no significant symptoms due to the presence of maternal thyroxine (T_4) from transplacental transfer. T_4 is responsible for the stimulation of protein synthesis as well as carbohydrate and lipid catabolism in many cells; as maternal T_4 wanes, metabolism is impaired and marked by a slowing of physical and mental activity (lethargy, poor feeding, constipation, hypotonia). Accumulation of matrix substances cutaneously and internally results in nonpitting edema (eg, **"puffy"** face), umbilical hernia, protruding tongue, and a large anterior fontanelle. In addition, T_4 is essential for normal brain development and myelination during early life, and infants are at risk of severe and **irreversible intellectual disability**.

Treatment with **levothyroxine** by age 2 weeks can normalize cognitive and physical development.

Therefore, universal newborn screening for congenital hypothyroidism is performed in the United States but not in all other countries.

(Choice A) Infants who are fed honey or exposed to spores from the soil are at risk for infantile botulism,

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not in all other countries.

(Choice A) Infants who are fed honey or exposed to spores from the soil are at risk for infantile botulism, which presents with constipation and flaccid paralysis. A large anterior fontanelle, umbilical hernia, and macroglossia are not seen.

(Choice B) Hypotonia and hypothyroidism are features of Down syndrome. However, the absence of other dysmorphic features (eg, upslanting palpebral fissures, bilateral epicanthal folds, single palmar crease) makes Down syndrome unlikely in this patient.

(Choice C) Galactosemia is caused by galactose-1-phosphate uridyltransferase deficiency. Patients with this condition present with jaundice, vomiting, hepatomegaly, and lethargy after ingesting galactose in breast milk or formula in the first few days of life. This patient was previously breastfeeding well and has no hepatomegaly.

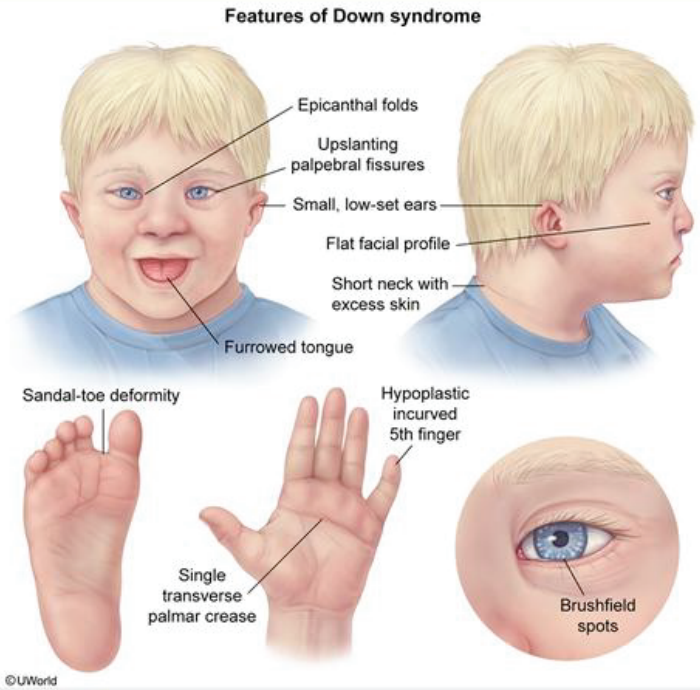
(Choice D) Hirschsprung disease is caused by abnormal migration of neural crest cells into the rectosigmoid colon. The lack of ganglion cells in this colon segment impedes gastrointestinal motility, resulting in failed meconium passage and bilious emesis in a newborn.

(Choice F) Phenylketonuria is most commonly caused by phenylalanine hydroxylase deficiency, resulting in hyperphenylalaninemia. It presents with developmental delay, light pigmentation, and a musty body

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in hyperphenylalaninemia. It presents with developmental delay, light pigmentation, and a musty body

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(Choice C) Galactosemia is caused by galactose-1-phosphate uridyltransferase deficiency. Patients with this condition present with jaundice, vomiting, hepatomegaly, and lethargy after ingesting galactose in breast milk or formula in the first few days of life. This patient was previously breastfeeding well and has no hepatomegaly.

(Choice D) Hirschsprung disease is caused by abnormal migration of neural crest cells into the rectosigmoid colon. The lack of ganglion cells in this colon segment impedes gastrointestinal motility, resulting in failed meconium passage and bilious emesis in a newborn.

(Choice F) Phenylketonuria is most commonly caused by phenylalanine hydroxylase deficiency, resulting in hyperphenylalaninemia. It presents with developmental delay, light pigmentation, and a musty body odor.

Educational objective:

Congenital hypothyroidism is usually asymptomatic at birth. After maternal T_4 wanes, infants develop constipation, lethargy, hypotonia, macroglossia, an umbilical hernia, and a large anterior fontanelle.

References

- Newborn screening for congenital hypothyroidism.
- Update of newborn screening and therapy for congenital hypothyroidism.

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A neonate is found to have increased TSH and low thyroxine (T4) on routine screening. He was born by vaginal delivery to a 32-year-old woman at 39 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals an enlarged thyroid gland in the normal position. Neck ultrasound confirms thyroid enlargement. Which of the following is the most likely cause of this patient's findings?

A. Maternal intake of levothyroxine
B. Maternal intake of propranolol
C. Maternal intake of propylthiouracil
D. Transplacental passage of thyroglobulin
E. Transplacental passage of TSH receptor–stimulating antibodies

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A neonate is found to have increased TSH and low thyroxine (T4) on routine screening. He was born by vaginal delivery to a 32-year-old woman at 39 weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination reveals an enlarged thyroid gland in the normal position. Neck ultrasound confirms thyroid enlargement. Which of the following is the most likely cause of this patient's findings?

A. ~~Maternal intake of levothyroxine~~ (13%)

B. ~~Maternal intake of propranolol~~ (3%)

✓ C. Maternal intake of propylthiouracil (47%)

D. ~~Transplacental passage of thyroglobulin~~ (11%)

E. Transplacental passage of TSH receptor–stimulating antibodies (22%)

Correct

47%
Answered correctly

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Common causes of congenital goiter			
Disorder	**TSH**	**FT4**	**Causes**
Hypothyroidism	↑	↓	• Genetic defect in thyroid hormone production • Maternal antithyroid medication (eg, propylthiouracil) • Excessive or deficient maternal iodine
Hyperthyroidism	↓	↑	• Transplacental TSH receptor–stimulating antibodies (neonatal Graves disease)

FT4 = free thyroxine.

This **neonate** has a **goiter**, or an enlarged thyroid gland, which is typically due to thyroid hormone dysregulation. The most commonly associated imbalance is **hypothyroidism**, as seen in this patient with elevated TSH and decreased thyroxine (T4).

One cause of neonatal hypothyroidism with a goiter is the **transplacental** passage of **maternal antithyroid medications** (eg, propylthiouracil, methimazole). Propylthiouracil is used to treat maternal hyperthyroidism (eg, Graves disease) because it inhibits thyroid peroxidase, thereby limiting oxidation and

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One cause of neonatal hypothyroidism with a goiter is the **transplacental** passage of **maternal antithyroid medications** (eg, propylthiouracil, methimazole). Propylthiouracil is used to treat maternal hyperthyroidism (eg, Graves disease) because it inhibits thyroid peroxidase, thereby limiting oxidation and incorporation of iodine into thyroid hormones; this medication also decreases conversion of peripheral T4 to triiodothyronine (T3).

Propylthiouracil crosses the placenta, inhibiting production of T4. Positive feedback caused by low T4 leads to increased TSH, which stimulates the thyroid and causes **diffuse gland enlargement**. TSH and T4 levels typically normalize after 1-2 weeks due to excretion of the maternally derived antithyroid medication. After elimination of propylthiouracil, neonates with mothers who have Graves disease may then develop transient hyperthyroidism (↓ TSH, ↑ T4) due to transplacental transfer of TSH receptor–stimulating antibodies **(Choice E)**, which can persist in the neonatal circulation for up to 3 months.

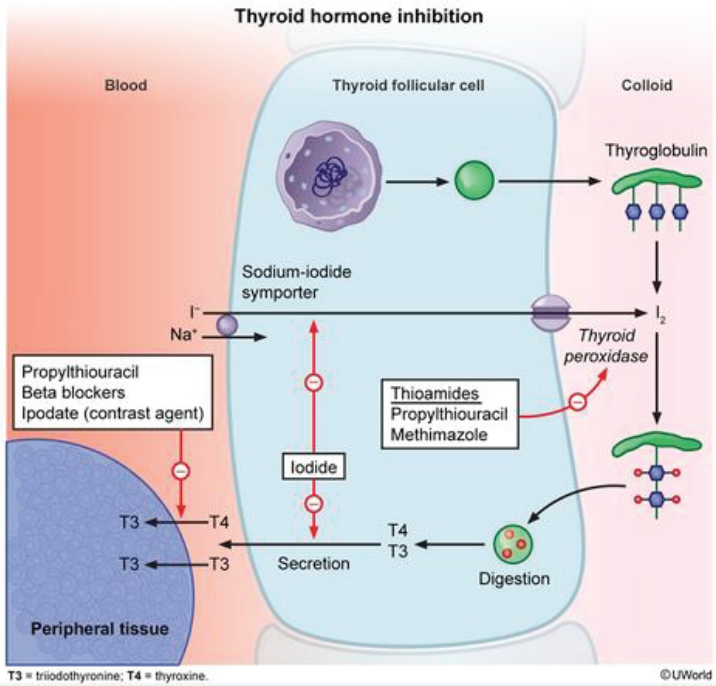
(Choice A) Levothyroxine (synthetic T4), like other thyroid hormones, does not readily cross the placenta. In addition, this medication treats, not causes, hypothyroidism.

(Choice B) Beta blockers (eg, propranolol) treat symptoms of hyperthyroidism attributable to increased beta-adrenergic activity (eg, palpitations, tachycardia). Although propranolol also decreases conversion of T4 to T3, this inhibitory effect is not strong enough to cause overt hypothyroidism and goiter at normal

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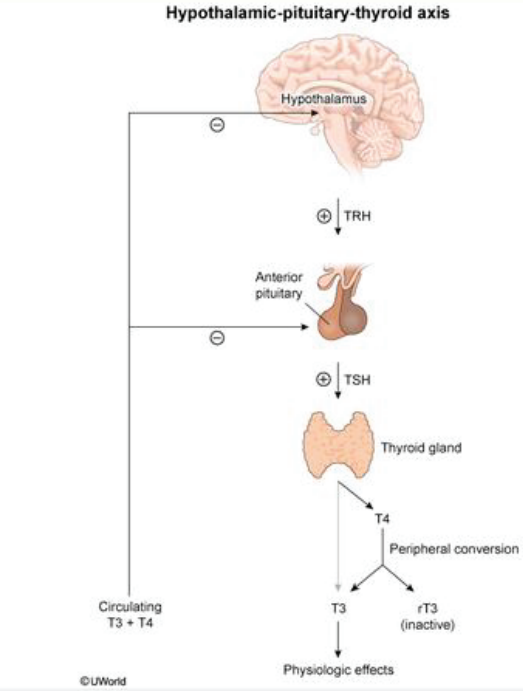


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(Choice B) Beta blockers (eg, propranolol) treat symptoms of hyperthyroidism attributable to increased beta-adrenergic activity (eg, palpitations, tachycardia). Although propranolol also decreases conversion of T4 to T3, this inhibitory effect is not strong enough to cause overt hypothyroidism and goiter at normal doses.

(Choice D) Thyroglobulin is a protein produced by the thyroid follicular cells and is involved in the storage and production of thyroid hormones. Thyroglobulin does not cross the placenta or cause hypothyroidism.

Educational objective:

Congenital goiter in the setting of hypothyroidism (ie, ↑ TSH, ↓ thyroxine) can be caused by transplacental passage of maternal antithyroid medications (eg, propylthiouracil), which inhibit thyroid peroxidase and are used to treat maternal hyperthyroidism.

References

- Congenital hypothyroidism.

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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A 67-year-old woman comes to the office due to polymyalgia rheumatica. She was diagnosed a year ago and has required supraphysiologic doses of prednisone to control her symptoms. The patient has no other medical conditions. She has adequate intake of calcium and vitamin D from her diet and supplements. The patient does not use tobacco or alcohol. Physical examination is unremarkable. Laboratory evaluation shows normal serum creatinine, 25-hydroxyvitamin D, and calcium levels. Bone density measured by dual x-ray absorptiometry (DXA) reveals a significant decline when compared to her bone density measured at age 65. Which of the following is most likely contributing to this patient's bone loss?

A. Increased activity of osteoprotegerin
B. Increased levels of insulin-like growth factor-1
C. Inhibition of osteoblast precursor cell replication and differentiation
D. Inhibition of receptor activator of nuclear factor kappa B
E. Suppression of parathyroid hormone release

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A. Increased activity of osteoprotegerin (7%)

B. ~~Increased levels of insulin-like growth factor-1~~ (2%)

✓ C. Inhibition of osteoblast precursor cell replication and differentiation (53%)

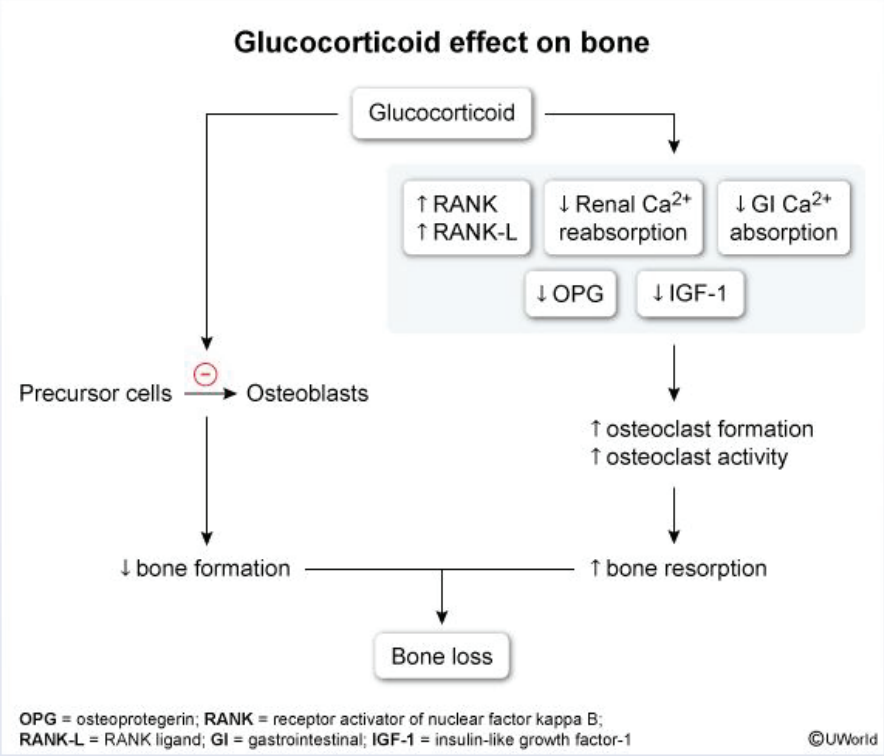
D. Inhibition of receptor activator of nuclear factor kappa B (34%)

E. ~~Suppression of parathyroid hormone release~~ (2%)

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Chronic or recurrent **glucocorticoid** (eg, prednisone) use, as is needed in patients with polymyalgia

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Chronic or recurrent **glucocorticoid** (eg, prednisone) use, as is needed in patients with polymyalgia rheumatica, is associated with an increased risk for **osteoporosis**. Glucocorticoids accelerate the development of osteoporosis by a number of mechanisms:

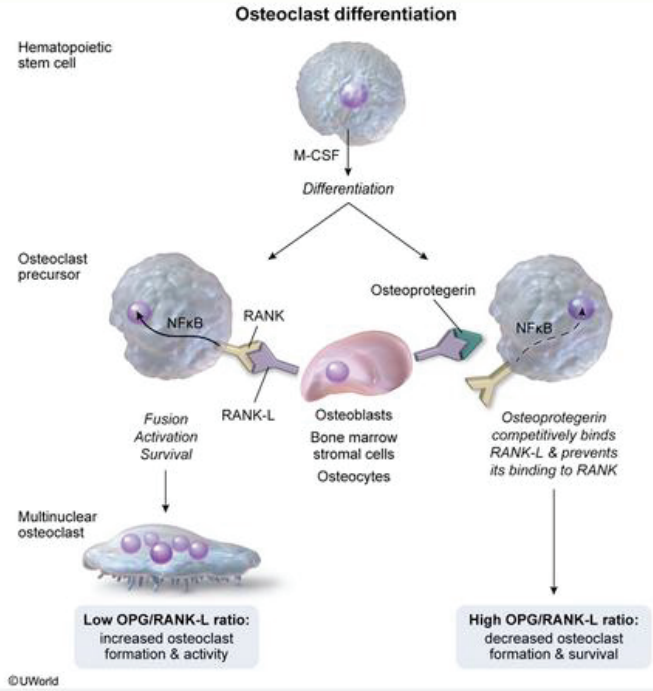
- **Decreased osteoblast effect:** Glucocorticoids **inhibit** the proliferation and differentiation of **osteoblast precursor cells**. They also induce increased rates of apoptosis in mature osteoblasts.
- **Increased osteoclast effect:** Osteoclast differentiation and activity are promoted by the receptor activator of nuclear factor kappa B (RANK)/RANK-ligand; this effect is inhibited by osteoprotegerin, which acts as a decoy receptor. Glucocorticoids increase the expression of RANK and RANK-ligand **(Choice D)** and decrease the expression of osteoprotegerin **(Choice A)**, leading to increased bone resorption.
- **Renal and intestinal calcium wasting:** Glucocorticoids suppress intestinal calcium absorption and renal calcium reabsorption, requiring increased release of calcium from bone to maintain calcium homeostasis.

(Choice B) Insulin-like growth factor-1 (IGF-1) is produced primarily in the liver but also locally in bone. It mediates many of the anabolic effects of growth hormone, including maintenance of bone mass. Glucocorticoids suppress (not increase) levels of IGF-1; in animal models, administration of exogenous

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Glucocorticoids suppress (not increase) levels of IGF-1; in animal models, administration of exogenous

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(Choice B) Insulin-like growth factor-1 (IGF-1) is produced primarily in the liver but also locally in bone. It mediates many of the anabolic effects of growth hormone, including maintenance of bone mass. Glucocorticoids suppress (not increase) levels of IGF-1; in animal models, administration of exogenous IGF-1 mitigates much of the bone loss associated with glucocorticoids.

(Choice E) Glucocorticoids alter the pattern of parathyroid hormone (PTH) secretion (eg, reduced tonic secretion and increased pulsatile PTH secretion), but overall secretion is only minimally changed. In general, bone loss is seen with excessive PTH secretion (ie, hyperparathyroidism) but not suppressed secretion.

Educational objective:

Chronic or recurrent glucocorticoid (eg, prednisone) use can lead to loss of bone density. Glucocorticoids inhibit replication and differentiation of osteoblast precursor cells, increase osteoclast activity, and promote intestinal and renal calcium wasting.

Pharmacology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

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A 64-year-old woman is brought to the emergency department due to confusion and lethargy. The patient was asymptomatic when her husband left for work in the morning, but when he arrived home, he found her in bed weak and disoriented. The patient's medical conditions include type 2 diabetes mellitus and hypertension, for which she takes multiple medications. She does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If her current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

A. Acarbose
B. Canagliflozin
C. Glyburide
D. Long-acting insulin
E. Metformin
F. Pioglitazone

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hypertension, for which she takes multiple medications. She does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If her current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

- A. Acarbose
- B. Canagliflozin
- C. Glyburide
- D. Long-acting insulin
- E. Metformin
- F. Pioglitazone
- G. Short-acting insulin

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Temperature is 37 C (98.6 F), blood pressure is 140/70 mm Hg, pulse is 74/min, and respirations are 18/min. On physical examination, the patient is somnolent but withdraws all extremities to pain. Laboratory testing shows an elevated serum C-peptide level. If her current condition is due to an antidiabetic drug, which of the following is the most likely culprit agent?

A. Acarbose (1%)
B. Canagliflozin (2%)
C. Glyburide (73%)
D. Long-acting insulin (4%)
E. Metformin (6%)
F. Pioglitazone (6%)
G. Short-acting insulin (5%)

Correct

73%
Answered correctly

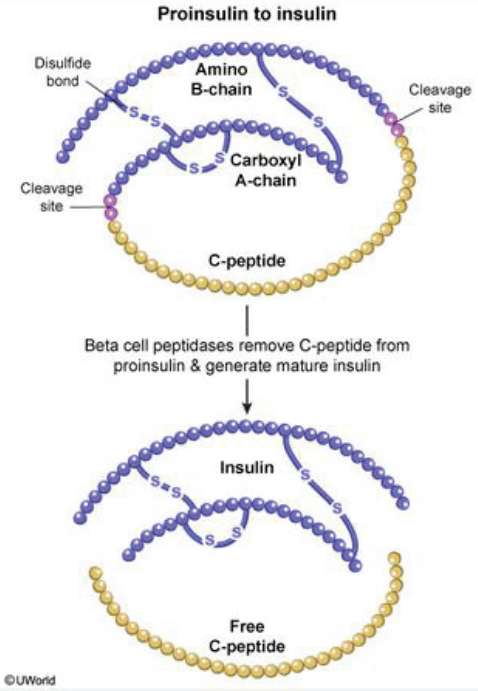
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This patient with type 2 diabetes mellitus has acute confusion and lethargy, which is consistent with symptomatic **hypoglycemia**, a common adverse effect of antidiabetic medications. Her **elevated C-peptide** level is further indicative of a medication that stimulates pancreatic insulin secretion independent of blood glucose levels, such as **sulfonylureas** (eg, glyburide) or meglitinides.

Insulin is synthesized in pancreatic beta cells as preproinsulin, which is guided by a signal peptide into the rough endoplasmic reticulum during translation. The signal peptide is then removed, converting preproinsulin to proinsulin. Protein folding and disulfide bond formation take place as proinsulin traverses the rough endoplasmic reticulum. Proinsulin is then transported to the Golgi apparatus, where it is packaged with proteolytic enzymes into insulin secretory granules and cleaved into mature insulin and C-peptide. **C-peptide and insulin** are then **co-secreted** from pancreatic beta cells in equimolar amounts.

When hypoglycemia is due to **excessive endogenous insulin** production (eg, sulfonylureas, meglitinides, insulinoma), C-peptide levels are elevated. In contrast, exogenous insulin and insulin analogs (ie, insulin-like polypeptides with alterations in the amino acid sequence to optimize pharmacokinetic properties) do not contain C-peptide. When hypoglycemia is induced by these agents, endogenous insulin secretion is suppressed and C-peptide levels are low **(Choices D and G)**.

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of

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Noninsulin antidiabetic agents for type 2 diabetes mellitus

Agent	Mechanism of action	Side effects
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis

New | Existing

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of

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• Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension
AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; K_{ATP} = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.		

New | Existing

(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of

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(Choice A) Acarbose inhibits alpha-glucosidase in the intestinal brush border, impairing the hydrolysis of polymeric carbohydrates and leading to decreased postprandial glucose absorption. Acarbose indirectly *decreases* endogenous insulin (and C-peptide) secretion by reducing postprandial hyperglycemia.

(Choices B, E, and F) Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease the reabsorption of filtered glucose. Major side effects include hypotension and urinary tract infection. Metformin is a biguanide that decreases hepatic glucose production, decreases intestinal glucose absorption, and increases peripheral glucose uptake and utilization. Thiazolidinediones (eg, pioglitazone) increase insulin sensitivity by increasing glucose utilization and decreasing glucose production in adipose tissue, muscle, and liver. These agents have a *low risk of hypoglycemia* and *do not increase endogenous insulin secretion*.

Educational objective:

Proinsulin is cleaved into mature insulin and C-peptide, which are co-secreted from pancreatic beta cells in equimolar amounts. Circulating levels of C-peptide can be used as a marker of endogenous insulin secretion. Sulfonylureas and meglitinides lower blood glucose by stimulating pancreatic insulin secretion; hypoglycemia due to these agents is associated with elevated C-peptide levels.

References

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A 1-week-old boy is brought to the emergency department with poor feeding, lethargy, and unusual "muscle movements" involving the left thumb and hand over the last 2 days. The patient's mother had appropriate prenatal care, a normal pregnancy, and took no medications other than prenatal vitamins. The infant's vital signs are normal, but unusual flexion of the left wrist and thumb and extension of the fingers are observed with cuff blood pressure measurement. Physical examination reveals a hypoplastic mandible, low-set ears, bifid uvula, and cleft palate. A chest x-ray reveals decreased soft-tissue attenuation in the right anterior mediastinum. These findings most likely suggest impaired development of which of the following embryonic structures?

A. Anterior neuropore
B. Foramen cecum
C. Rathke pouch
D. Second pharyngeal cleft
E. Third pharyngeal pouch

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movements" involving the left thumb and hand over the last 2 days. The patient's mother had appropriate prenatal care, a normal pregnancy, and took no medications other than prenatal vitamins. The infant's vital signs are normal, but unusual flexion of the left wrist and thumb and extension of the fingers are observed with cuff blood pressure measurement. Physical examination reveals a hypoplastic mandible, low-set ears, bifid uvula, and cleft palate. A chest x-ray reveals decreased soft-tissue attenuation in the right anterior mediastinum. These findings most likely suggest impaired development of which of the following embryonic structures?

- A. Anterior neuropore (3%)
- B. Foramen cecum (1%)
- C. Rathke pouch (5%)
- D. Second pharyngeal cleft (12%)
- ✓ E. Third pharyngeal pouch (77%)

Correct

77%

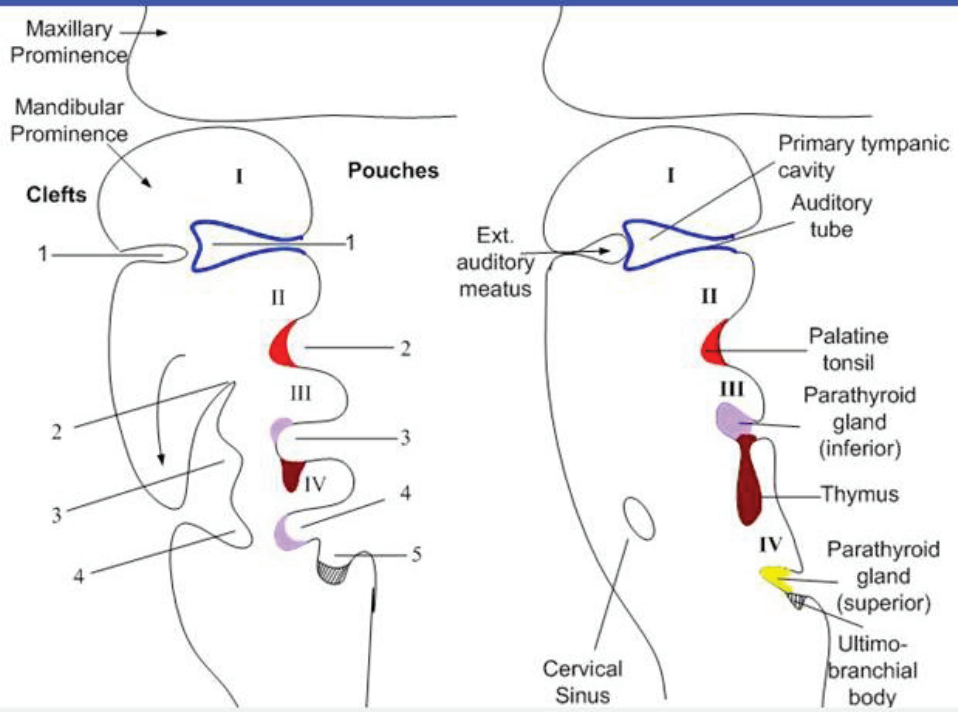
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Sinus body

A **22q11.2 microdeletion** underlies the spectrum of physical features seen in DiGeorge syndrome (DGS). Embryologically, the neural crest fails to migrate into the derivatives of the **third** (affects inferior **parathyroid** and thymus) and fourth (affects superior parathyroid) pharyngeal/branchial pouches. The consequent parathyroid and thymic hypoplasia results in **hypocalcemia** and T cell deficiency, respectively.

The hypocalcemia in DGS leads to increased neuromuscular excitability, which manifests as tetany, carpopedal spasms, or seizures. Tapping on the facial nerve usually elicits **twitching of the nose and lips (Chvostek sign)**, and inflation of the blood pressure cuff leads to **carpal spasm (Trousseau sign)**. Normally, the thymic shadow is visible on a newborn's x-ray. Its absence reflects thymic hypoplasia, which leads to T cell dysfunction and results in recurrent viral, fungal, and protozoan infections.

Conotruncal cardiac anomalies (eg, interrupted aortic arch, truncus arteriosus) may also result from failure of neural crest migration. If there is additional involvement of the first and second pharyngeal/branchial pouches, patients with DGS may have features such as hypertelorism, short palpebral fissures, micrognathia, bifid uvula, and cleft palate.

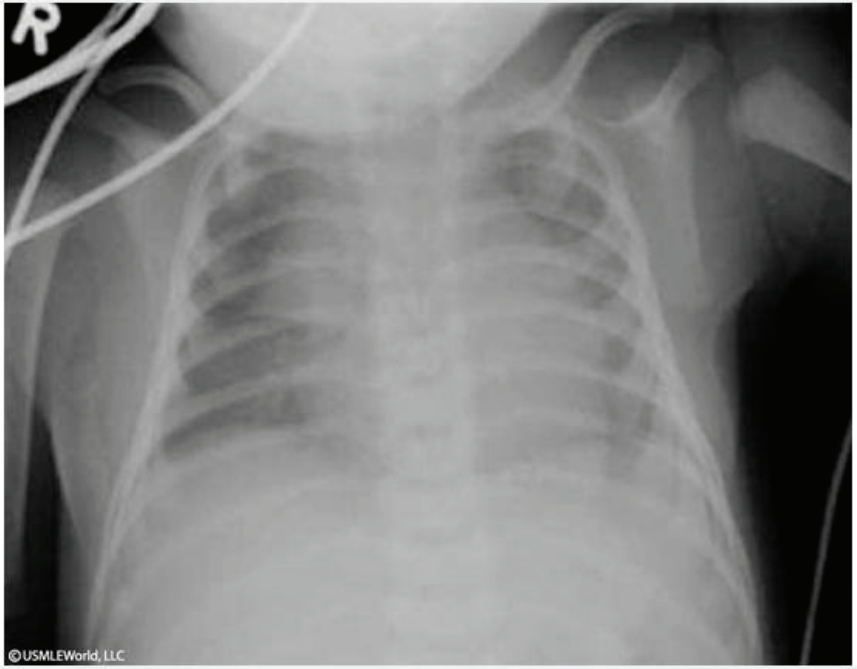
(Choice A) Failure of the anterior neuropore to close leads to neural tube defects such as anencephaly. Neural tube defects can be prevented with maternal folic acid supplementation.

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Thymus x-ray Thymus x-ray



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micrognathia, bifid uvula, and cleft palate.

(Choice A) Failure of the anterior neuropore to close leads to neural tube defects such as anencephaly. Neural tube defects can be prevented with maternal folic acid supplementation.

(Choice B) The foramen cecum is a depression on the tongue that represents the embryological remnant of the superior end of the obliterated thyroglossal duct. A persistent duct results in a thyroglossal cyst that presents as a midline neck mass.

(Choice C) Rathke pouch represents an invaginated oral ectoderm that eventually develops into the anterior pituitary. Craniopharyngiomas arise from remnants of this pouch and can result in hypopituitarism, hydrocephalus, and diabetes insipidus, but not hypocalcemia.

(Choice D) The second branchial cleft (ie, second pharyngeal groove) is normally obliterated in utero. Persistence leads to a branchial cleft cyst between the angle of the mandible and sternocleidomastoid muscle.

Educational objective:
DiGeorge syndrome results from maldevelopment of the third (inferior parathyroid and thymus) and fourth (superior parathyroid) pharyngeal/branchial pouches. Subsequent parathyroid and thymic hypoplasia results in hypocalcemia and T cell deficiency.

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micrognathia, bifid uvula, and cleft palate.

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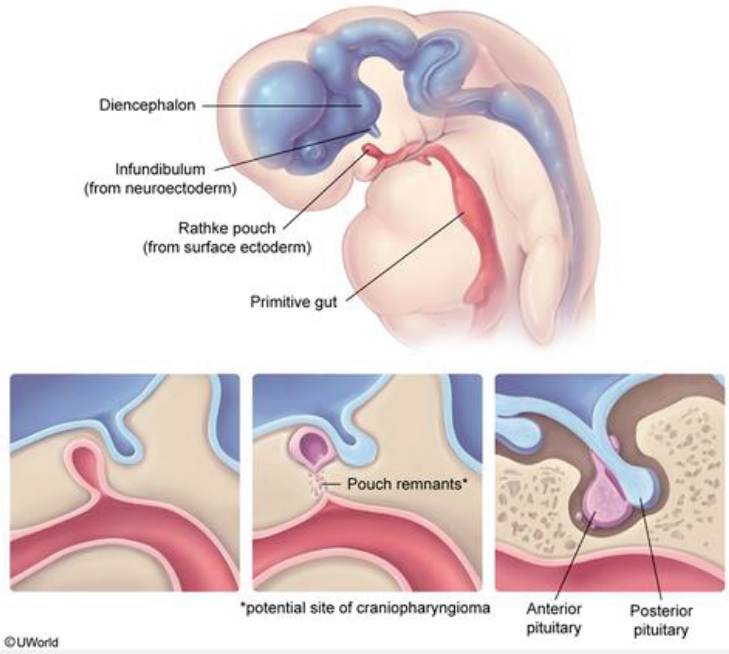
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micrognathia, bifid uvula, and cleft palate.

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Pituitary embryology



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A 1-week-old boy is brought to the emergency department due to recurrent vomiting and poor feeding. The infant was born at term via spontaneous vaginal delivery with no complications. Temperature is 36.7 C (98 F), blood pressure is 58/30 mm Hg, pulse is 180/min, and respirations are 40/min. On examination, the patient is tired appearing with a sunken anterior fontanelle and dry mucous membranes. The remainder of the examination is unremarkable. Laboratory results are as follows:

Serum chemistry	
Sodium	122 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Which of the following additional laboratory findings are most likely to be seen in this patient?

Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone

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Potassium	5.1 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Which of the following additional laboratory findings are most likely to be seen in this patient?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone
A.	↓	↓	↑	↑
B.	↓	↑	↑	↓
C.	↓	↓	↑	↓
D.	↓	↓	↓	↑
E.	↑	↓	↑	↑

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Potassium	5.1 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Which of the following additional laboratory findings are most likely to be seen in this patient?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone	
A.	↓	↓	↑	↑	(64%)
B.	↓	↑	↑	↓	(7%)
C.	↓	↓	↑	↓	(16%)
D.	↓	↓	↓	↑	(5%)
E.	↑	↓	↑	↑	(6%)

Correct

64%
Answered correctly

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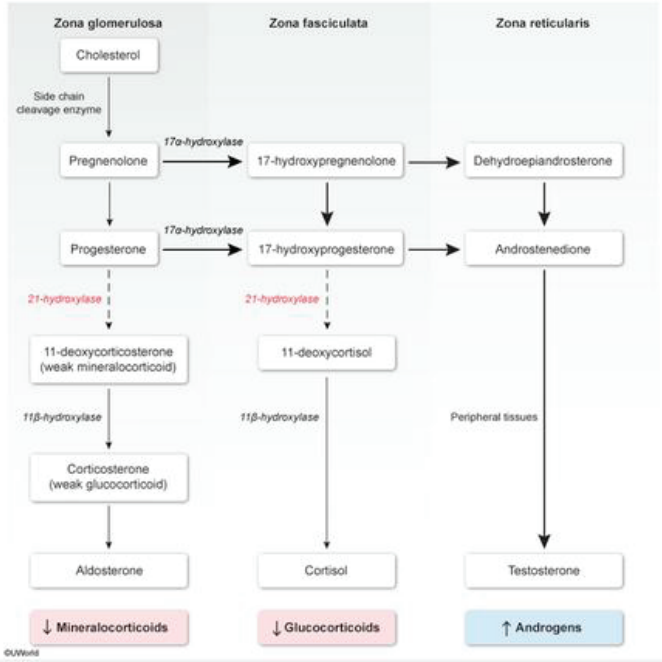
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21-hydroxylase deficiency



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This infant is dehydrated (ie, sunken fontanelle, dry mucous membranes) with hypotension, hyponatremia, and hyperkalemia. These findings are consistent with classic **congenital adrenal hyperplasia** (CAH) due to **21-hydroxylase deficiency**.

Patients with 21-hydroxylase deficiency cannot convert 17-hydroxyprogesterone (17-OHP) into 11-deoxycortisol, which results in **elevated 17-OHP** and **decreased aldosterone and cortisol** production. Corticosteroid precursors accumulate and are diverted toward **excess adrenal androgen** biosynthesis. Low cortisol levels (ie, loss of negative feedback) also trigger **increased ACTH** production by the anterior pituitary, which further stimulates the formation of adrenal androgens **(Choice D)**.

Although affected girls are usually identified at birth due to ambiguous genitalia (virilization) from excess androgens, boys have normal genitalia and typically are identified at age 1-2 weeks with vomiting, **hypotension**, **hyponatremia**, and **hyperkalemia** due to lack of sufficient mineralocorticoids **(salt wasting)**. Cortisol deficiency causes hypoglycemia and further impairs the ability to maintain blood pressure.

(Choice B) CAH due to 17 alpha-hydroxylase deficiency prevents the conversion of progesterone to 17-OHP, resulting in low 17-OHP, cortisol, and adrenal androgen production. In contrast to this case,

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pressure.

(Choice B) CAH due to 17 alpha-hydroxylase deficiency prevents the conversion of progesterone to 17-OHP, resulting in low 17-OHP, cortisol, and adrenal androgen production. In contrast to this case, hypertension and hypokalemia occur with 17 alpha-hydroxylase deficiency due to increased mineralocorticoids.

(Choice C) Adrenal steroid synthesis is also impaired with primary adrenal insufficiency (ie, Addison disease); however, autoimmune destruction of the adrenal glands is unlikely to occur in the first week of life, making 21-hydroxylase deficiency a much more likely cause of adrenal crisis in this patient.

(Choice E) An ACTH-secreting tumor causes increased synthesis of cortisol and its precursors (eg, 17-OHP). Cushing disease is rare in newborns and would be associated with glucocorticoid-induced hypertension (not hypotension) and subsequent inhibition of aldosterone.

Educational objective:
Classic 21-hydroxylase deficiency causes decreased cortisol and aldosterone production with increased adrenal androgen production. In boys, this deficiency presents 1-2 weeks after birth with vomiting, hypotension, hyponatremia, and hyperkalemia due to salt wasting; genitalia are normal. In girls, it presents at birth with ambiguous genitalia.

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A 2-year-old boy is brought to the office by his parents. He is currently toilet-training during the day and at nighttime. After he urinated in the toilet last night, his parents forgot to flush the toilet and noticed that the boy's urine turned black overnight. The child has no significant past medical history and takes no medications. He can say 2-word sentences, follow 2-step directions, and jump with 2 feet off the ground. Examination shows a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

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Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

A. Leucine to acetoacetate
B. Phenylalanine to tyrosine
C. Serine to cysteine
D. Tyrosine to fumarate
E. Valine to glutamic acid

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Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

A. Leucine to acetoacetate (6%)
B. Phenylalanine to tyrosine (19%)
C. Serine to cysteine (15%)
D. Tyrosine to fumarate (54%)
E. Valine to glutamic acid (3%)

Correct

54%
Answered correctly

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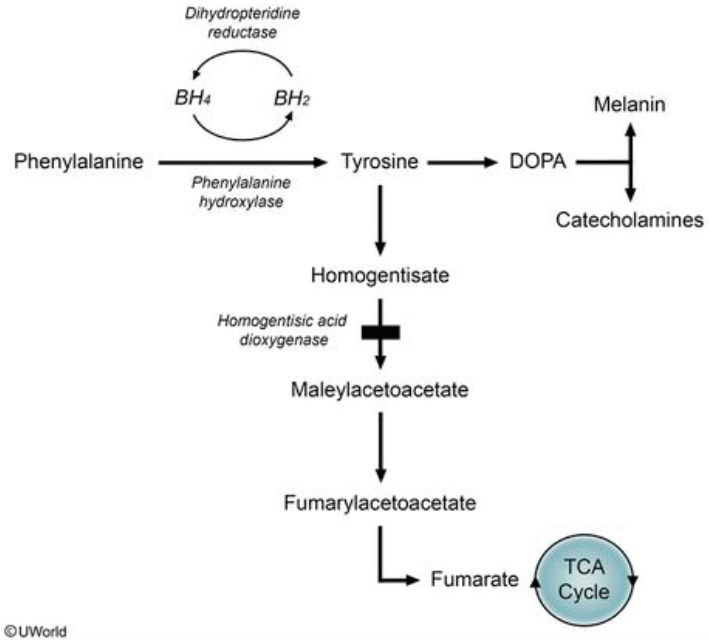
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Alkaptonuria



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Alkaptonuria is an **autosomal recessive** disorder of **tyrosine metabolism**. Deficiency of homogentisic acid dioxygenase blocks homogentisic acid metabolism, preventing the conversion of tyrosine to fumarate. Homogentisic acid accumulates in the body and is excreted in the urine, imparting a **black color** to the **urine** if allowed to sit and undergo oxidation. In patients with alkaptonuria, the retained homogentisic acid selectively binds to collagen in connective tissues, tendons, and cartilage. This leads to "**ochronosis**," a blue-black pigmentation most evident in the ears, nose, and cheeks, and **ochronotic arthropathy**, which typically manifests during adulthood.

(Choice A) Leucine is a branched-chain amino acid that is elevated in maple syrup urine disease. Isoleucine and valine are also increased. Impaired metabolism of these amino acids leads to cerebral edema, seizures, and a sweet smell of the urine.

(Choice B) Conversion of phenylalanine to tyrosine is defective in phenylketonuria and usually occurs due to a defect in phenylalanine hydroxylase. Undiagnosed and untreated phenylketonuria results in significant intellectual disability not seen in this patient.

(Choice C) Impaired renal cystine (a homodimer of cysteine) transport leads to cystinuria, a disease characterized by flank pain, hematuria, and renal stones in childhood or adolescence

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intellectual disability not seen in this patient.

(Choice C) Impaired renal cystine (a homodimer of cysteine) transport leads to cystinuria, a disease characterized by flank pain, hematuria, and renal stones in childhood or adolescence.

(Choice E) Sickle cell anemia results from the substitution of valine for glutamic acid due to a single-nucleotide polymorphism. This mutation leads to loss of red cell elasticity, polymerization of sickle hemoglobin, and sickling of red blood cells, which results in vasoocclusive crises.

Educational objective:

Alkaptonuria is an autosomal recessive disorder in which the lack of homogentisic acid dioxygenase blocks the metabolism of tyrosine, leading to an accumulation of homogentisic acid. Clinical features include a black urine color when exposed to air, a blue-black pigmentation on the face, and ochronotic arthropathy.

References

- Alkaptonuria.

Biochemistry	Endocrine, Diabetes & Metabolism	Alkaptonuria
Subject	System	Topic

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A 36-year-old man with type 1 diabetes mellitus comes to the office due to recurrent hypoglycemic episodes. He previously had difficulty controlling his high blood glucose levels, but over the past several weeks his blood glucose has intermittently dropped to <50 mg/dL with accompanying symptoms of tremulousness and headache. There have been no recent changes in his diet, activity level, insulin dosage, or other medical therapy. The patient's other medical conditions include chronic kidney disease from diabetic nephropathy. His estimated glomerular filtration rate has declined to 20 mL/min in recent months, and he is under consideration for initiation of hemodialysis. Physical examination findings are unchanged from the previous office visit 3 months ago. Which of the following is most likely contributing to this patient's current glycemic disturbances?

A. Decreased hepatic glucose production
B. Decreased renal insulin clearance
C. Increased pancreatic insulin secretion
D. Increased renal glucose excretion
E. Increased tissue insulin sensitivity

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weeks his blood glucose has intermittently dropped to <50 mg/dL with accompanying symptoms of tremulousness and headache. There have been no recent changes in his diet, activity level, insulin dosage, or other medical therapy. The patient's other medical conditions include chronic kidney disease from diabetic nephropathy. His estimated glomerular filtration rate has declined to 20 mL/min in recent months, and he is under consideration for initiation of hemodialysis. Physical examination findings are unchanged from the previous office visit 3 months ago. Which of the following is most likely contributing to this patient's current glycemic disturbances?

A. Decreased hepatic glucose production (4%)
B. Decreased renal insulin clearance (59%)
C. Increased pancreatic insulin secretion (1%)
D. Increased renal glucose excretion (32%)
E. Increased tissue insulin sensitivity (1%)

Correct

59%

56 secs

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Insulin is a peptide hormone that has both **renal and hepatic clearance**. Degradation of circulating insulin in the kidneys is dependent on an adequate glomerular filtration rate (GFR), which allows for delivery of insulin to the proximal tubule cells where it is broken down. **Chronic kidney disease** (CKD) causes **decreased GFR**, which impairs insulin clearance.

In patients with normal pancreatic function, hypoglycemia is avoided because pancreatic insulin production decreases and circulating insulin levels rapidly return to baseline. However, patients taking **exogenous insulin** are at increased **risk of hypoglycemia** if there is no decrease in dosage to compensate for renal failure.

In light of this patient's worsening CKD, his symptomatic hypoglycemia is likely due to **reduced renal insulin clearance** and a prolonged insulin effect.

(Choice A) Advanced CKD leads to reduced gluconeogenesis in the kidney, not the liver. Hepatic gluconeogenesis is inhibited by inflammatory cytokine release (eg, sepsis), heavy alcohol use, and beta blockers.

(Choice C) Patients with type 1 diabetes typically have minimal to no secretory reserve and cannot increase insulin in response to physiologic stimuli.

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insulin clearance and a prolonged insulin effect.

(Choice A) Advanced CKD leads to reduced gluconeogenesis in the kidney, not the liver. Hepatic gluconeogenesis is inhibited by inflammatory cytokine release (eg, sepsis), heavy alcohol use, and beta blockers.

(Choice C) Patients with type 1 diabetes typically have minimal to no secretory reserve and cannot increase insulin in response to physiologic stimuli.

(Choice D) Increased renal glucose excretion can cause glucosuria; however, this occurs in the setting of significant hyperglycemia (not hypoglycemia). In addition, this patient's low glomerular filtration rate would be expected to reduce renal glucose excretion.

(Choice E) Insulin sensitivity is decreased (not increased) in CKD due to the accumulation of urea and other metabolic toxins.

Educational objective:
Insulin has both renal and hepatic clearance. In patients with advanced chronic kidney disease and diabetes mellitus, decreased renal clearance of insulin can lead to symptomatic hypoglycemia if exogenous insulin doses are not adjusted based on the change in renal function.

References

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A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

A. Galactitol to tagatose
B. Galactose to galactitol
C. Glucose to sorbitol
D. Glucose-6-phosphate to 6-phosphogluconolactone
E. Pyruvate to lactate

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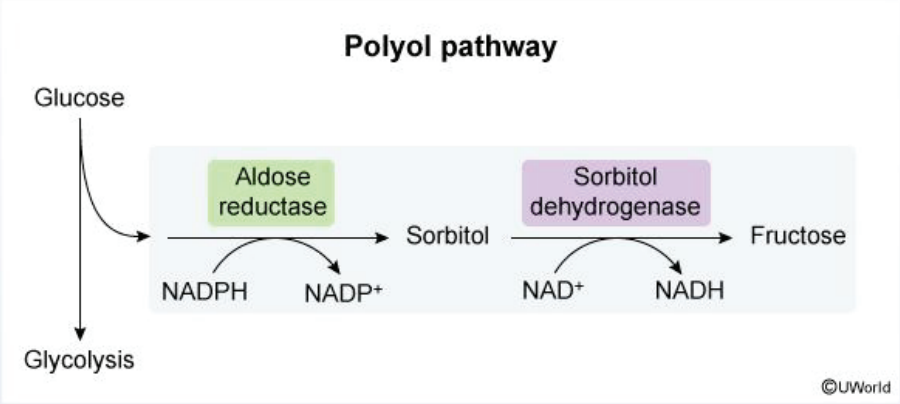
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A. Galactitol to tagatose (0%)
B. Galactose to galactitol (12%)
C. Glucose to sorbitol (83%)
D. Glucose-6-phosphate to 6-phosphogluconolactone (1%)
E. Pyruvate to lactate (1%)

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This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-induced damage because they are unable to regulate glucose transport when circulating levels are high.

Multiple metabolic pathways are involved in the pathogenesis of hyperglycemia-induced tissue damage:

- **Advanced glycosylation end-products (AGEs):** Glucose can nonenzymatically attach to proteins and lipids, forming reversible glycosylation products that slowly stabilize into irreversible products.

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Multiple metabolic pathways are involved in the pathogenesis of hyperglycemia-induced tissue damage.

- **Advanced glycosylation end-products (AGEs):** Glucose can nonenzymatically attach to proteins and lipids, forming reversible glycosylation products that slowly stabilize into irreversible products. Under hyperglycemic conditions, AGEs accumulate and facilitate deposition of LDL in blood vessel walls and inflammatory cell invasion that causes atherosclerosis and microangiopathic complications. High glucose levels in the aqueous humor may also induce nonenzymatic glycation of lens proteins, which contributes to cataract formation.
- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase

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(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase deficiency), excess galactitol is produced, which causes cataracts in newborns.

(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

(Choice E) Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Excess lactate forms in hypoxic states, causing metabolic acidosis.

Educational objective:
In hyperglycemic states, aldose reductase converts glucose to sorbitol at a rate faster than sorbitol can be metabolized. Sorbitol accumulates in certain cells such as lens cells, causing an influx of water and resulting in osmotic cellular injury. Depletion of NADPH by aldose reductase also increases oxidative stress, which accelerates development of cataracts and diabetic microvascular complications (eg, neuropathy, retinopathy).

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A 3-day-old boy is brought to the office due to poor feeding, vomiting, and progressive lethargy. The parents also report that his diapers have a "burnt sugar smell" differing from their previous children's diapers. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical problems. Physical examination shows a lethargic infant with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

A. Galactose
B. Leucine
C. Methionine
D. Phenylalanine
E. Tyrosine

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A 3-day-old boy is brought to the office due to poor feeding, vomiting, and progressive lethargy. The parents also report that his diapers have a "burnt sugar smell" differing from their previous children's diapers. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical problems. Physical examination shows a lethargic infant with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

A. Galactose (8%)
B. Leucine (71%)
C. Methionine (2%)
D. Phenylalanine (14%)
E. Tyrosine (2%)

Correct

71% Answered correctly

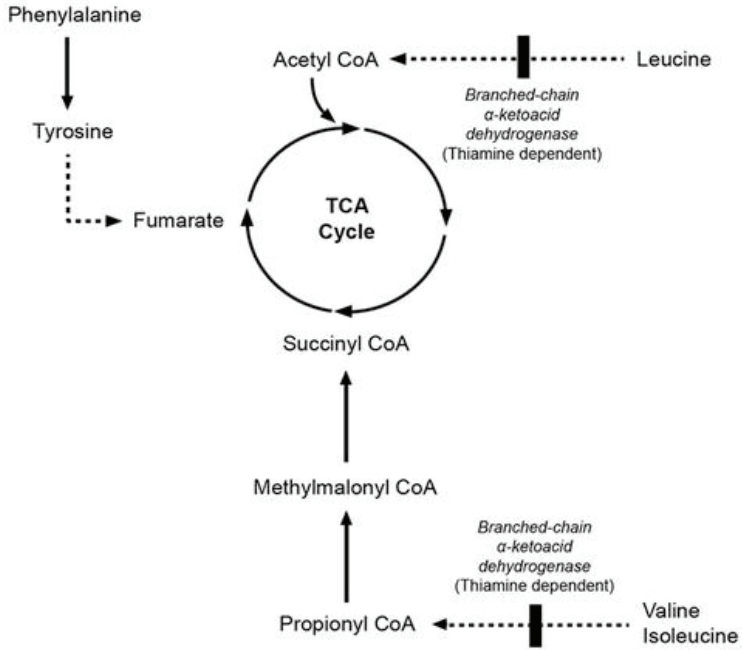
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This infant has symptoms typical of **maple syrup urine disease** (MSUD), an autosomal recessive inborn error of metabolism due to branched-chain α-ketoacid dehydrogenase complex (BCKDC) deficiency. This enzyme normally allows for the breakdown of **leucine**, **isoleucine**, and **valine** into substrates for entry into the TCA cycle.

BCKDC deficiency is **neurotoxic** primarily due to elevated levels of leucine. Infants present in the first few days of life with progressive irritability, poor feeding, lethargy, and increased muscle tone. The urine characteristically has a sweet, **"maple syrup" odor**. Diagnosis can be confirmed by the presence of **elevated branched-chain amino acid levels**. Therapy consists of **dietary restriction** of branched-chain amino acids, but patients remain at lifelong risk for neurotoxicity in the setting of intercurrent illnesses and fasting.

(Choice A) Galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase deficiency. The buildup of galactose (normally found in breast milk and regular infant formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine

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formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine β-synthase, resulting in elevated levels of homocysteine and methionine. Restriction of methionine for these patients is one aspect of therapy.

(Choice D) Phenylketonuria is an autosomal recessive disorder characterized by phenylalanine hydroxylase deficiency, leading to hyperphenylalaninemia. Untreated patients develop intellectual disability, seizures, decreased hair/skin pigmentation, and a "musty" odor.

(Choice E) Dietary tyrosine restriction may be beneficial for patients with hypertyrosinemia (progressive liver and renal disease) or alkaptonuria (pigmented osteoarthritis).

Educational objective:

Maple syrup urine disease classically presents with irritability, dystonia, poor feeding, and a "maple syrup" scent to the patient's urine within the first few days of life. Dietary restriction of branched-chain amino acids (eg, leucine, isoleucine, valine) is the hallmark of treatment.

References

- Branched-chain amino acid metabolism: From rare Mendelian diseases to more common disorders.

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 4-year-old boy is brought to the clinic after his mother noticed he was developing pubic hair. The boy had a recent growth spurt and is now taller than his 5-year-old brother. The patient's preschool teacher recently mentioned he has body odor after he runs or plays. Height is at the 95th percentile for age, and weight is at the 80th percentile. Examination reveals sparse growth of long, pigmented hair at the base of the penis and in both axillae. Testes are present bilaterally and appear normal. Laboratory assessment reveals high serum concentrations of 17-hydroxyprogesterone and testosterone.

Item 1 of 2

Which of the following is most likely present in this patient?

A. Adrenal cortical hyperplasia
B. Adrenal medullary hyperplasia
C. Leydig cell tumor

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A 4-year-old boy is brought to the clinic after his mother noticed he was developing pubic hair. The boy had a recent growth spurt and is now taller than his 5-year-old brother. The patient's preschool teacher recently mentioned he has body odor after he runs or plays. Height is at the 95th percentile for age, and weight is at the 80th percentile. Examination reveals sparse growth of long, pigmented hair at the base of the penis and in both axillae. Testes are present bilaterally and appear normal. Laboratory assessment reveals high serum concentrations of 17-hydroxyprogesterone and testosterone.

Item 1 of 2

Which of the following is most likely present in this patient?

A. Adrenal cortical hyperplasia
B. Adrenal medullary hyperplasia
C. Leydig cell tumor
D. Pituitary adenoma
E. Seminoma

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Item 1 of 2

Which of the following is most likely present in this patient?

- A. Adrenal cortical hyperplasia (79%)
- B. Adrenal medullary hyperplasia (4%)
- C. ~~Leydig cell tumor~~ (8%)
- D. ~~Pituitary adenoma~~ (7%)
- E. ~~Seminoma~~ (0%)

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21-Hydroxylase deficiency clinical syndromes			
	Classic, salt wasting	**Classic, non–salt wasting***	**Nonclassic, late onset**
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		
*Also called simple virilizing form.			

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Deficiency of 21-hydroxylase is the most common form of **congenital adrenal hyperplasia** and leads to impaired conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Excess 17-OHP is shunted away from cortisol synthesis toward androgen production. **ACTH increases** due to the decline in cortisol levels and has a trophic effect on adrenal cortical cells, causing **adrenal cortical hyperplasia**.

Depending on the residual enzyme activity, 21-hydroxylase deficiency can present as 3 distinct clinical syndromes of differing severity. This patient most likely has the **classic, non–salt-wasting** (ie, simple virilizing) form of the disease. Because 21-hydroxylase is not completely absent (as in the most severe form), sufficient mineralocorticoids and glucocorticoids are maintained to avoid salt wasting such that patients have normal blood pressure and electrolytes. Due to **adrenal androgen overproduction**, girls with this variant are often identified at birth due to ambiguous genitalia. **Boys** appear normal at birth and typically present around **age 2-4** with **early virilization** (eg, body odor, pubic/axillary hair). Exposure to high levels of sex hormones also induces an early pubertal growth spurt that manifests as **accelerated linear growth** at a young age.

In all forms of 21-hydroxylase deficiency, patients have **increased 17-OHP** and androgen levels. Adrenal androgens (eg, dehydroepiandrosterone and androstenedione) undergo peripheral conversion to testosterone, which explains this patient's **high testosterone** level.

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testosterone, which explains this patient's **high testosterone** level.

(Choice B) Adrenal medullary hyperplasia is a precursor lesion for pheochromocytoma characterized by increased catecholamine production. Presenting signs include hypertension, tachycardia, and sweating (not virilization).

(Choice C) Leydig cell tumors produce excess testosterone and can present with precocious puberty in young boys (eg, early testicular/phallic enlargement). A testicular mass is typically palpated on examination.

(Choice D) Production of excess LH and FSH by pituitary adenomas can lead to increased testosterone but not increased 17-OHP levels. Pituitary adenomas producing excess ACTH can lead to excess adrenal androgen production; however, symptoms of excess cortisol production (Cushing syndrome) such as growth deceleration and weight gain would predominate.

(Choice E) A seminoma is a testicular tumor most commonly found in adolescents and adults. These tumors are derived from the seminiferous tubules and present with a testicular mass, not virilization and elevated testosterone.

Educational objective:

Deficiency of 21-hydroxylase causes adrenal cortical hyperplasia due to excess stimulation of the adrenal

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(Choice C) Leydig cell tumors produce excess testosterone and can present with precocious puberty in young boys (eg, early testicular/phallic enlargement). A testicular mass is typically palpated on examination.

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(Choice E) A seminoma is a testicular tumor most commonly found in adolescents and adults. These tumors are derived from the seminiferous tubules and present with a testicular mass, not virilization and elevated testosterone.

Educational objective:
Deficiency of 21-hydroxylase causes adrenal cortical hyperplasia due to excess stimulation of the adrenal cortex by ACTH. The classic, non–salt-wasting form presents in boys age 2-4 with early virilization, accelerated linear growth, and elevated levels of 17-hydroxyprogesterone and androgens.

Pathology Endocrine, Diabetes & Metabolism Congenital adrenal hyperplasia

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Item 2 of 2

After initial assessment, the appropriate interventions are initiated. Targeted suppression of which of the following hormones is the best next step to limit androgen overproduction?

- A. Adrenocorticotropic hormone
- B. Cortisol
- C. Luteinizing hormone
- D. Prolactin
- E. Testosterone

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Item 2 of 2

After initial assessment, the appropriate interventions are initiated. Targeted suppression of which of the following hormones is the best next step to limit androgen overproduction?

- ✓ A. Adrenocorticotropic hormone (52%)
- B. ~~Cortisol~~ (4%)
- C. ~~Luteinizing hormone~~ (21%)
- D. ~~Prolactin~~ (1%)
- E. ~~Testosterone~~ (19%)

Correct

52%
Answered correctly

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Explanation

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Patients with congenital adrenal hyperplasia (CAH) due to **21-hydroxylase deficiency** have impaired cortisol synthesis. Subsequent lack of feedback causes the hypothalamus to **increase adrenocorticotropic hormone (ACTH) secretion** by the anterior pituitary. This results in stimulation of the adrenal cortex and **adrenal androgen overproduction** (eg, dehydroepiandrosterone, androstenedione).

Treatment of 21-hydroxylase deficiency involves low (ie, physiologic) doses of exogenous corticosteroids that **suppress ACTH secretion** via negative feedback mechanisms. Without excess ACTH stimulation, androgen production by the adrenal cortex decreases.

(Choice B) Deficiency of 21-hydroxylase impairs cortisol synthesis; further suppression of cortisol production could precipitate an adrenal crisis (eg, hypoglycemia, hypotension).

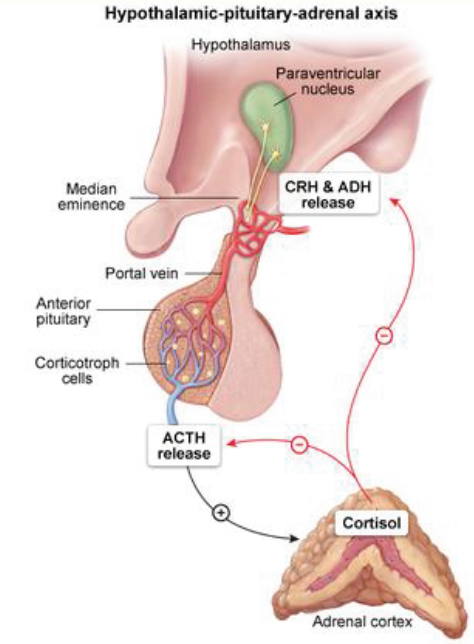
(Choice C) Luteinizing hormone (LH) stimulates the testes to produce testosterone. Decreasing LH levels would decrease testosterone production by the testes but would not affect excess adrenal androgen production in CAH.

(Choice D) Hyperprolactinemia disrupts GnRH secretion, which leads to decreased testosterone production and hypogonadism. Prolactin suppression would further elevate testosterone levels and would not be beneficial in this patient.

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(Choice C) Luteinizing hormone (LH) stimulates the testes to produce testosterone. Decreasing LH levels would decrease testosterone production by the testes but would not affect excess adrenal androgen production in CAH.

(Choice D) Hyperprolactinemia disrupts GnRH secretion, which leads to decreased testosterone production and hypogonadism. Prolactin suppression would further elevate testosterone levels and would not be beneficial in this patient.

(Choice E) This patient's symptoms are the result of excessive production of adrenal androgens (eg, dehydroepiandrosterone and androstenedione), which can subsequently undergo peripheral conversion to testosterone. Blockade of testosterone alone would not be sufficient to prevent progression of this patient's symptoms, as the androgenic effects of these testosterone precursors would remain unopposed.

Educational objective:
Treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency involves low doses of exogenous corticosteroids to suppress excess ACTH secretion, which reduces production of androgens by the adrenal cortex.

Pathology Endocrine, Diabetes & Metabolism Congenital adrenal hyperplasia

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A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

A. Brain
B. Erythrocytes
C. Heart muscle
D. Renal cortex
E. Skeletal muscle

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A. Brain (13%)
B. Erythrocytes (79%)
C. Heart muscle (1%)
D. Renal cortex (1%)
E. Skeletal muscle (4%)

Correct

79%
Answered correctly

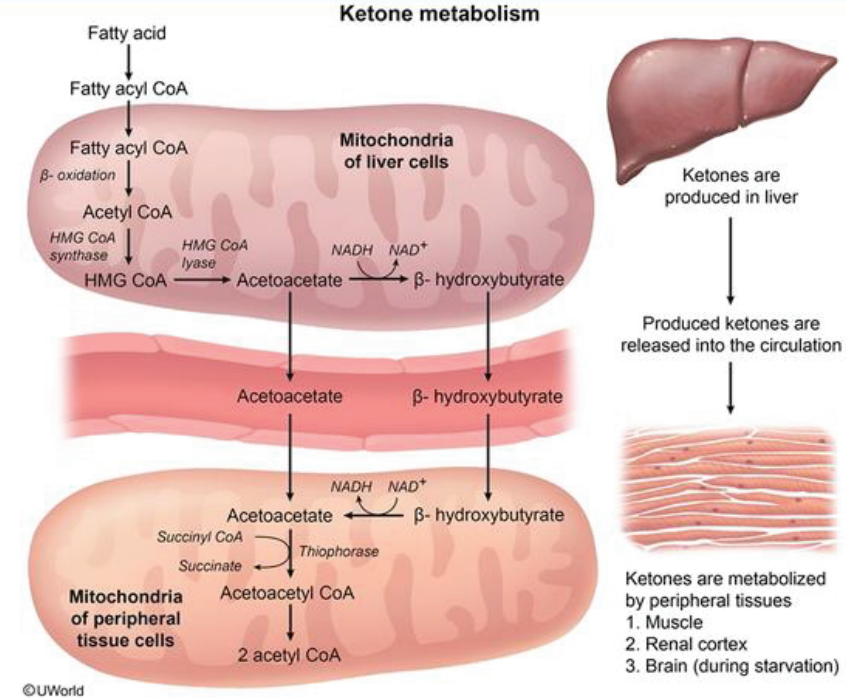
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After about 12-18 hours of **fasting**, the body's glycogen stores are depleted and **gluconeogenesis** is required to maintain blood glucose levels. As fasting continues, the body limits its reliance on gluconeogenesis in an effort to conserve protein and resorts instead to **ketone body synthesis**. Ketone bodies are generated in the liver from fatty acids and yield energy when converted to acetyl CoA in the **mitochondria** of target cells.

The brain, kidneys, cardiac muscle, and skeletal muscle **(Choices A, C, D & E)** can all utilize ketones for energy. In the initial stages of fasting, the heart and skeletal muscle consume primarily ketone bodies to preserve glucose for the brain, but in prolonged starvation, even the brain will utilize ketone bodies for the majority of its energy needs. However, erythrocytes cannot use ketone bodies for energy because they lack mitochondria. The liver is also unable to utilize ketone bodies for energy because it lacks the enzyme succinyl CoA-acetoacetate CoA transferase (thiophorase), which is required to convert acetoacetate to acetoacetyl CoA.

Educational objective:

When glycogen stores are depleted during fasting, ketone bodies are produced in the liver and can be used as an energy source in the mitochondria of peripheral tissues. The brain preferentially uses glucose, but will utilize ketones for most of its energy needs during prolonged starvation. Erythrocytes lack mitochondria

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Educational objective:
When glycogen stores are depleted during fasting, ketone bodies are produced in the liver and can be used as an energy source in the mitochondria of peripheral tissues. The brain preferentially uses glucose, but will utilize ketones for most of its energy needs during prolonged starvation. Erythrocytes lack mitochondria and are unable to use ketones.

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A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in the past 3 months. The patient has no other medical problems and takes no medication. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 104/min and regular. The thyroid gland is diffusely enlarged and nontender on palpation. Laboratory studies show markedly decreased serum TSH and elevated thyroxine levels. Methimazole monotherapy is initiated. Two months later, her symptoms had resolved. The treatment most likely improved this patient's condition by directly inhibiting which of the following processes?

A. Colloid production

B. Coupling of iodotyrosines

C. Iodide uptake by the thyroid gland

D. Peripheral thyroxine to triiodothyronine conversion

E. Triiodothyronine/thyroxine effect on target tissues

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A 22-year-old woman comes to the office due to palpitations, weight loss, and insomnia. She has lost 7 kg (15.4 lb) in the past 3 months. The patient has no other medical problems and takes no medication. She does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 104/min and regular. The thyroid gland is diffusely enlarged and nontender on palpation. Laboratory studies show markedly decreased serum TSH and elevated thyroxine levels. Methimazole monotherapy is initiated. Two months later, her symptoms had resolved. The treatment most likely improved this patient's condition by directly inhibiting which of the following processes?

A. Colloid production (1%)

B. Coupling of iodotyrosines (74%)

C. Iodide uptake by the thyroid gland (7%)

D. ~~Peripheral thyroxine to triiodothyronine conversion~~ (14%)

E. ~~Triiodothyronine/thyroxine effect on target tissues~~ (1%)

74%

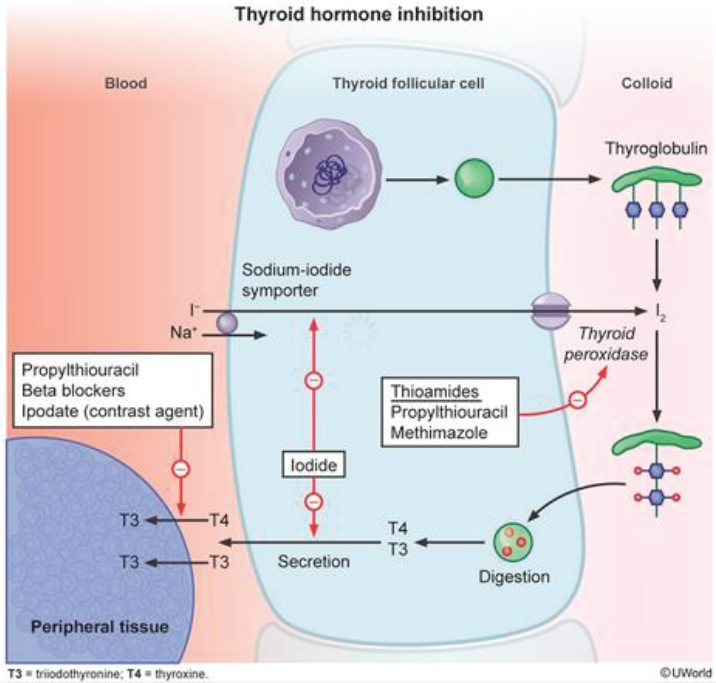
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Thyroid follicular cells take up inorganic iodide (iodide trapping) against a concentration gradient using a sodium-iodide symporter. Iodide is then released into the thyroid follicular lumen, where it is oxidized to iodine radical by thyroid peroxidase. Iodine then binds to tyrosine residues (organification) in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Coupling of MIT and DIT produces triiodothyronine (T3; MIT coupled with DIT) and thyroxine (T4; two DITs coupled). The thyroid follicular cells then engulf thyroglobulin, which contains the iodinated tyrosine compounds, via pinocytosis. In the thyroid cytoplasm, T3 and T4 (collectively, thyroid hormones) are removed from the rest of the thyroglobulin and secreted from the basolateral border.

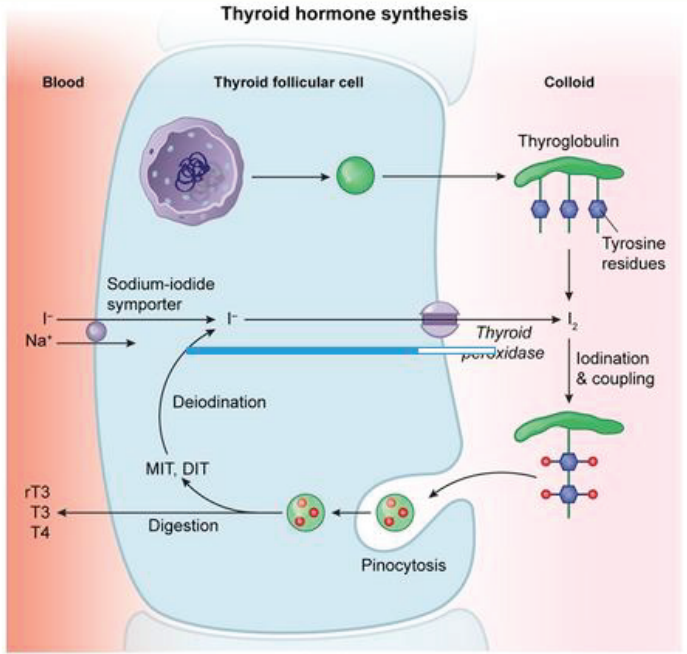
This patient with elevated T4 and suppressed TSH has primary **hyperthyroidism**. Methimazole and propylthiouracil are **thioamide drugs** used for treating hyperthyroidism. They **inhibit thyroid peroxidase**, the enzyme responsible for both **iodine organification** and **coupling of iodotyrosines**. Propylthiouracil also decreases the peripheral conversion of T4 to the active hormone T3, although methimazole does not have this effect **(Choice D)**.

(Choice A) Colloid is a gelatinous material in the follicular lumen that consists mainly of thyroglobulin. The production of colloid is regulated primarily by TSH; it is not dependent on thyroid peroxidase and is not inhibited by thioamides.

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have this effect **(Choice D)**.

(Choice A) Colloid is a gelatinous material in the follicular lumen that consists mainly of thyroglobulin. The production of colloid is regulated primarily by TSH; it is not dependent on thyroid peroxidase and is not inhibited by thioamides.

(Choice C) Iodide uptake is upregulated by TSH. Perchlorate and pertechnetate are competitive inhibitors of the sodium-iodide symporter.

(Choice E) Hyperthyroidism is characterized by increased sensitivity to catecholamines due to the thyroid hormone–mediated upregulation of beta-adrenergic receptors. Beta blockers help decrease the target organ effects of thyroid hormones, and certain ones (eg, propranolol) also decrease the peripheral conversion of T4 to T3.

Educational objective:
Thioamides (eg, methimazole, propylthiouracil) decrease the formation of thyroid hormones via inhibition of thyroid peroxidase, the enzyme responsible for both iodine organification and coupling of iodotyrosines. Propylthiouracil also decreases the peripheral conversion of T4 to T3.

Pharmacology Endocrine, Diabetes & Metabolism Hyperthyroidism

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A 61-year-old woman comes to the office due to a neck lump. She is otherwise in good health and has no other symptoms. Temperature is 36.7 C (98 F), blood pressure is 115/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the left lobe of the thyroid. Laboratory results show a normal serum TSH level. Thyroid ultrasonography reveals a 2-cm, hypoechoic thyroid nodule with increased central blood flow. Fine-needle aspiration biopsy shows clusters of cells with large, overlapping nuclei containing sparse, finely dispersed chromatin. Numerous intranuclear inclusion bodies and grooves are also seen. Which of the following is the most likely diagnosis in this patient?

A. Anaplastic carcinoma
B. Colloid nodule
C. Follicular adenoma
D. Follicular carcinoma
E. Medullary carcinoma
F. Papillary carcinoma

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A. Anaplastic carcinoma (12%)
B. Colloid nodule (1%)
C. Follicular adenoma (10%)
D. Follicular carcinoma (9%)
E. Medullary carcinoma (9%)
F. Papillary carcinoma (55%)

Correct

55%

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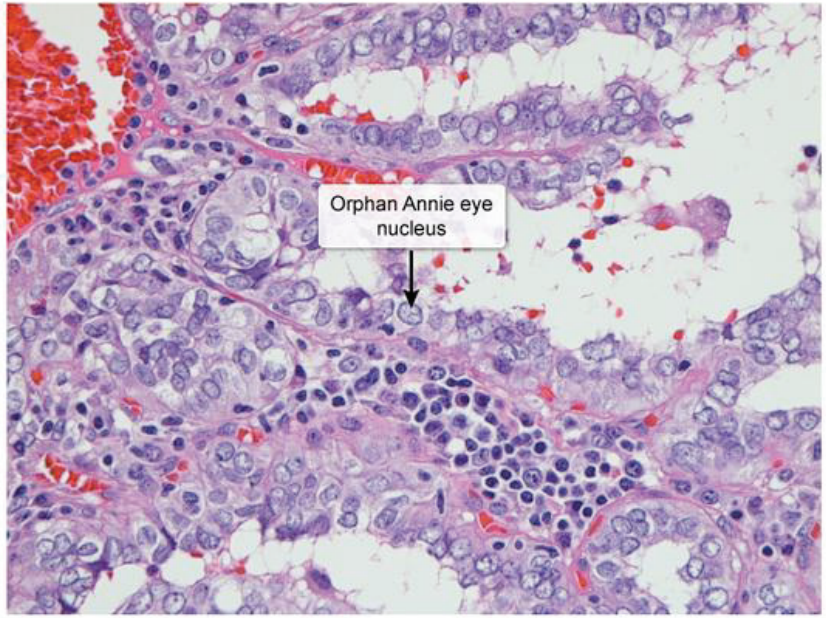
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Papillary thyroid carcinoma



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The 4 main types of primary thyroid carcinoma include papillary, follicular, medullary (derived from the parafollicular calcitonin-secreting C cells), and anaplastic. The papillary type is most common, accounting for >70% of cases. Risk factors include a positive family history of thyroid cancer and radiation exposure (especially during childhood).

Papillary carcinoma cells are characteristically large with overlapping nuclei containing **finely dispersed chromatin**, giving them an empty or ground-glass appearance (sometimes termed **Orphan Annie eye** nuclei after a cartoon character whose eyes were drawn without pupils or irises). Numerous **intranuclear inclusions and grooves** (arrow) can be seen due to invagination of the nuclear membrane. Psammoma bodies (laminated calcium deposits) may also be found within the tumor.

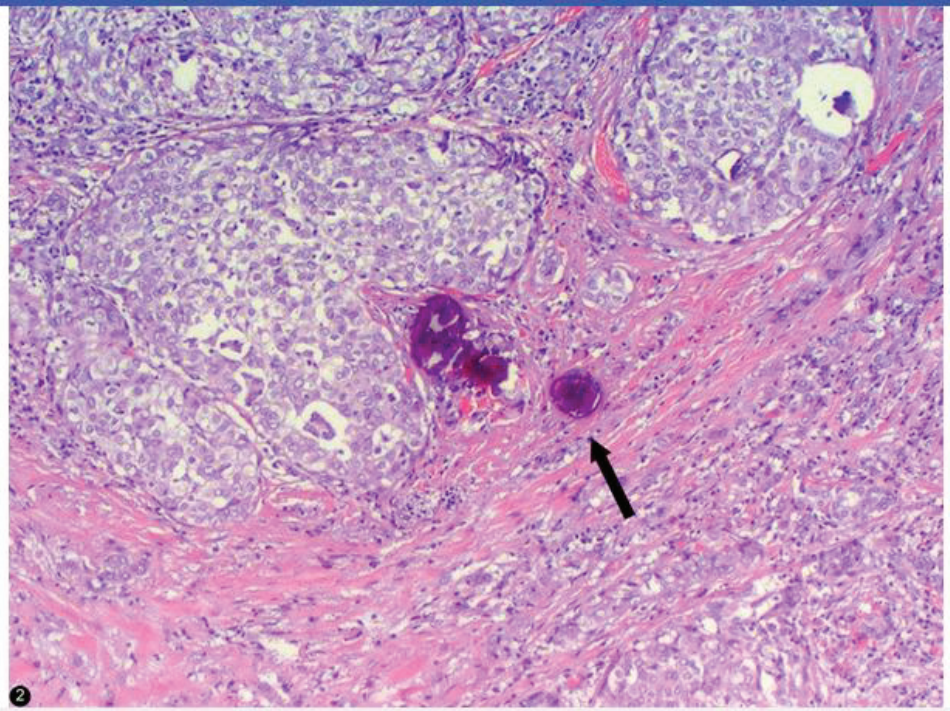
(Choice A) Anaplastic thyroid cancer is an aggressive tumor with a very poor prognosis. It is most common in older patients (age >60). Cytologic features include markedly pleomorphic cells, including irregular giant cells and biphasic spindle cells.

(Choice B) Most benign thyroid nodules are colloid nodules formed from focal hyperplasia of normal thyroid follicular cells. On cytopathology, a colloid nodule consists of variable-sized thyroid follicles, colloid, and macrophages.

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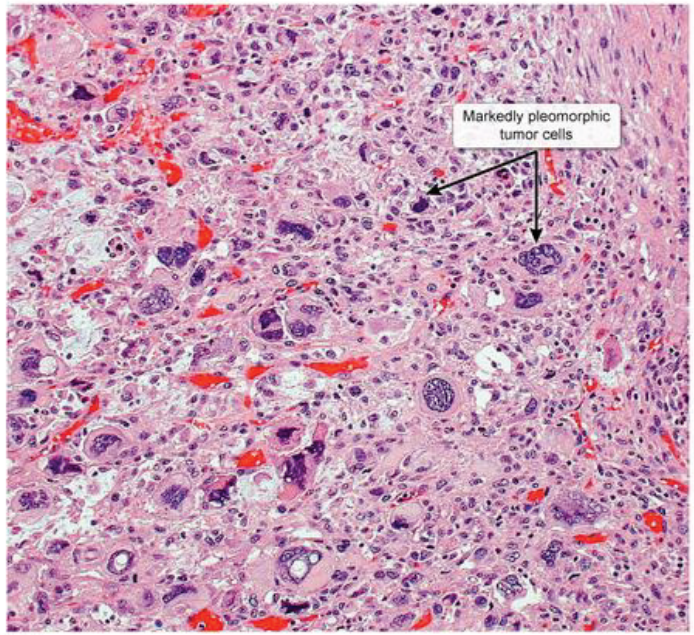
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Anaplastic thyroid carcinoma



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irregular giant cells and biphasic spindle cells.

(Choice B) Most benign thyroid nodules are colloid nodules formed from focal hyperplasia of normal thyroid follicular cells. On cytopathology, a colloid nodule consists of variable-sized thyroid follicles, colloid, and macrophages.

(Choices C and D) Follicular neoplasms lack the characteristic nuclear features and psammoma bodies found in papillary tumors. Distinguishing a benign follicular adenoma from a well-differentiated follicular cancer depends on the presence of vascular and capsular invasion, which cannot be determined on a fine-needle aspiration specimen.

(Choice E) Medullary thyroid cancer appears histologically as polygonal or spindle-shaped cells with a slightly granular cytoplasm that stains for calcitonin. Extracellular amyloid deposits (arrow) consisting of calcitonin polypeptide may also be seen. Medullary thyroid cancer is a component of multiple endocrine neoplasia types 2A and 2B.

Educational objective:
Papillary thyroid cancer is the most common type of thyroid cancer. Characteristic findings on histopathology include large cells with nuclei containing finely dispersed chromatin, giving an empty or ground-glass appearance (Orphan Annie eye), and intranuclear inclusions or grooves.

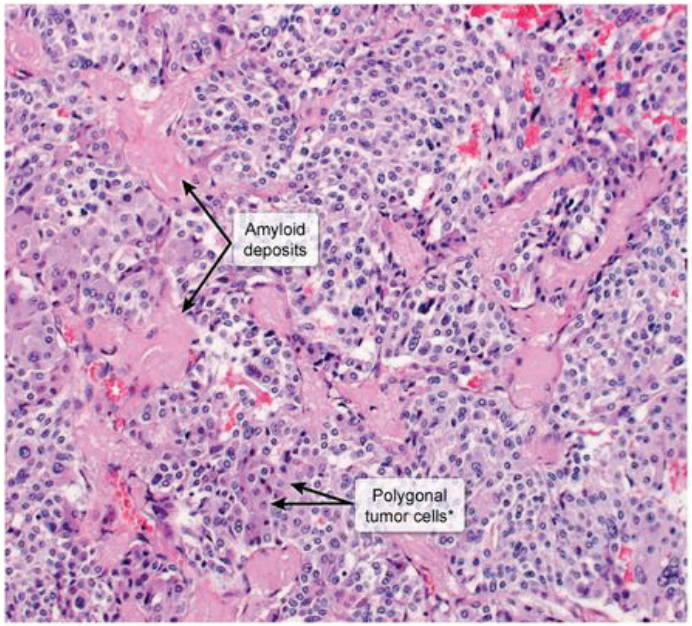
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irregular giant cells and biphasic spindle cells

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Medullary thyroid carcinoma



*Derived from C (parafollicular) cells

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A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years. They have no children. Infertility evaluation is begun, and laboratory studies show a low sperm count. A more thorough evaluation elucidates a rare genetic abnormality that leads to permanently inactive FSH receptors. Which of the following substances is most likely decreased in this patient?

A. FSH
B. LH
C. Inhibin B
D. Testosterone
E. DHEA

Submit

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A 25-year-old man comes to the physician because he and his wife have been unable to conceive for the last 2 years. They have no children. Infertility evaluation is begun, and laboratory studies show a low sperm count. A more thorough evaluation elucidates a rare genetic abnormality that leads to permanently inactive FSH receptors. Which of the following substances is most likely decreased in this patient?

- A. ~~FSH~~ (1%)
- B. ~~LH~~ (2%)
- ✓ C. Inhibin B (79%)
- D. Testosterone (12%)
- E. DHEA (4%)

Correct

79% Answered correctly

37 secs Time Spent

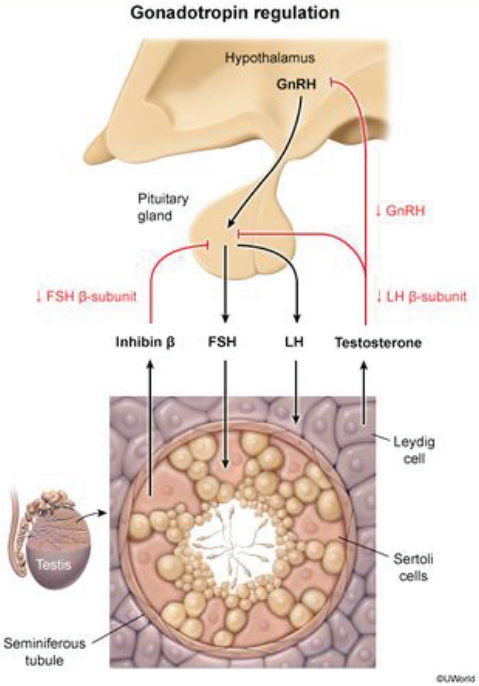
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Explanation

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Pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the gonadotroph cells in the anterior pituitary. LH stimulates the release of testosterone from the Leydig cells in the interstitium of the testicles, and FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules of the testicles. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

FSH also stimulates the Sertoli cells to produce androgen-binding protein locally, within the seminiferous tubules. This androgen-binding protein is responsible for the high local testosterone concentration and is different from sex hormone-binding globulin, which is found in the blood. High local levels of testosterone and FSH are necessary for spermatogenesis. Defective FSH receptors will prevent spermatogenesis and cause low inhibin B levels, because FSH is responsible for both spermatogenesis and inhibin B production.

(Choice A) FSH levels will be high in patients with FSH receptor defects because there is no negative feedback from inhibin B; inhibin B cannot be produced without proper functioning of the FSH pathway.

(Choices B and D) LH and testosterone levels are likely to be normal in this patient because FSH does not play a role in either LH or testosterone feedback. Since the FSH receptor defect is isolated, this patient will have normal testosterone and LH levels.

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cause low inhibin B levels, because FSH is responsible for both spermatogenesis and inhibin B production.

(Choice A) FSH levels will be high in patients with FSH receptor defects because there is no negative feedback from inhibin B; inhibin B cannot be produced without proper functioning of the FSH pathway.

(Choices B and D) LH and testosterone levels are likely to be normal in this patient because FSH does not play a role in either LH or testosterone feedback. Since the FSH receptor defect is isolated, this patient will have normal testosterone and LH levels.

(Choice E) The circulating levels of other androgens such as DHEA, DHEAS, and androstenedione are also not affected by FSH.

Educational objective:
LH stimulates the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells in the seminiferous tubules. Testosterone and inhibin B induce negative feedback on LH and FSH production, respectively.

Physiology	Endocrine, Diabetes & Metabolism	Infertility
Subject	System	Topic

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A 24-year-old woman, gravida 1 para 1, comes to the office for postpartum follow-up 2 weeks after a term vaginal delivery. Her baby is doing well, but she is concerned because she has not yet lactated. The patient knew she would lose weight and be tired after the baby was born, but she feels excessive fatigue and has had significant weight loss. She also has nausea, loss of appetite, and postural dizziness. The patient has no headaches, visual problems, cold intolerance, constipation, or polyuria. On examination, she appears fatigued and has mild pallor. Laboratory tests are drawn the next morning at 8:00 AM, with the following results:

Hemoglobin	9.6 g/dL
Sodium	130 mEq/L
Cortisol, serum	4 µg/dL
Free T_4	1.0 ng/dL
TSH	0.2 µU/mL

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Sodium	mEq/L
Cortisol, serum	4 µg/dL
Free T_4	1.0 ng/dL
TSH	0.2 µU/mL

Which of the following pathologic processes is most likely responsible for this patient's symptoms?

A. Glandular hemorrhage
B. Inflammation
C. Ischemic necrosis
D. Malignant infiltration
E. Non-malignant infiltration

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Cortisol, serum	4 µg/dL
Free T_4	1.0 ng/dL
TSH	0.2 µU/mL

Which of the following pathologic processes is most likely responsible for this patient's symptoms?

A. Glandular hemorrhage (21%)
B. Inflammation (1%)
C. Ischemic necrosis (72%)
D. Malignant infiltration (1%)
E. Non-malignant infiltration (2%)

Correct

72%

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Hypopituitarism	
Etiology	**Pituitary causes** • Mass lesions (primary or metastatic) • Infiltration (eg, lymphocytic hypophysitis) • Hemorrhage (pituitary apoplexy) • Ischemic infarction (Sheehan syndrome) **Hypothalamic lesions** (eg, sarcoidosis, infection, radiation therapy)
Clinical presentation	**ACTH deficiency** • Hypotension, weight loss, hypoglycemia **Hypothyroidism** • Fatigue, cold intolerance, slowed deep-tendon reflexes **Gonadotropins** • Women: Amenorrhea, infertility • Men: Infertility, loss of libido

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This patient has signs of **panhypopituitarism** with failure of lactation, central hypothyroidism, and adrenal

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This patient has signs of **panhypopituitarism** with failure of lactation, central hypothyroidism, and adrenal insufficiency. In the setting of a recent delivery, this most likely represents **ischemic necrosis** of the **pituitary gland** (Sheehan syndrome). During pregnancy, the pituitary enlarges due to estrogen-induced hyperplasia of the lactotrophs. However, the blood supply to the pituitary does not increase proportionally. As a result, the enlarged pituitary is vulnerable to ischemia in case of systemic hypotension due to **peripartum hemorrhage** (which this patient likely experienced given her low hemoglobin).

The most common manifestation of Sheehan syndrome is failure of lactation due to prolactin deficiency. It also commonly causes hypocortisolism and hypothyroidism. Manifestations of thyroid deficiency may take a few weeks to develop due to the long circulating half-life of thyroxine (5-7 days) and peripheral conversion of thyroxine (T4) to T3. Cortisol deficiency manifests rapidly, however, with nausea, postural hypotension, fatigue, and weight loss.

(Choice A) Pituitary apoplexy is due to sudden hemorrhage into the pituitary, usually in the setting of a preexisting pituitary adenoma. It usually presents with acute severe headache, ophthalmoplegia, and altered sensorium.

(Choice B) Lymphocytic hypophysitis is the most common inflammatory condition of the pituitary and typically occurs during late pregnancy or the early postpartum period. In contrast to Sheehan syndrome,

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(Choice B) Lymphocytic hypophysitis is the most common inflammatory condition of the pituitary and typically occurs during late pregnancy or the early postpartum period. In contrast to Sheehan syndrome, the presentation is acute with severe headaches and visual field defects.

(Choice D) Primary pituitary cancer is extremely rare, although the pituitary is prone to metastases due to its rich vascular supply. These patients typically present with tumor mass effects (eg, headache, bitemporal hemianopsia).

(Choice E) Non-malignant infiltrative lesions such as sarcoidosis and histiocytosis X mainly involve the suprasellar region, where they compress the hypothalamus and pituitary stalk. This disrupts the normal hypothalamic dopaminergic suppression of prolactin secretion, leading to increased prolactin levels and possible galactorrhea. Central diabetes insipidus may also be seen with resulting hypernatremia.

Educational objective:
High estrogen levels during pregnancy cause enlargement of the pituitary gland without a proportional increase in blood supply. Peripartum hypotension can cause ischemic necrosis of the pituitary leading to panhypopituitarism (Sheehan syndrome). Patients commonly develop failure of lactation due to deficiency of prolactin.

References

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A 29-year-old nulligravid woman comes to the office due to a 2-month history of worsening bilateral nipple discharge that stains her bra. The patient has felt no breast mass and has had no breast pain, headaches, or vision changes. Her last menstrual period was 3 months ago, and home pregnancy tests have been negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

A. Increased estrogen effect on the pituitary
B. Inhibition of gonadotropin-releasing hormone secretion
C. Inhibition of hypothalamic dopaminergic neurons
D. Stimulation of pituitary dopamine receptors
E. Stimulation of thyrotropin-releasing hormone receptors

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discharge that stains her bra. The patient has felt no breast mass and has had no breast pain, headaches, or vision changes. Her last menstrual period was 3 months ago, and home pregnancy tests have been negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

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B. Inhibition of gonadotropin-releasing hormone secretion
C. Inhibition of hypothalamic dopaminergic neurons
D. Stimulation of pituitary dopamine receptors
E. Stimulation of thyrotropin-releasing hormone receptors

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negative. Previously, she had regular menstrual cycles at 28-day intervals. The patient has no other medical conditions and takes no medications. Vital signs are within normal limits. On physical examination, visual fields are intact by confrontation. A whitish fluid can be expressed bilaterally on nipple compression. There are no breast masses or lymphadenopathy. Pelvic examination reveals no abnormalities. Serum beta-hCG testing is negative. Brain imaging shows a 0.6-cm pituitary mass. Pharmacotherapeutic treatment is begun, and on a follow-up visit the patient reports that her symptoms are improving. Which of the following is the most likely mechanism of action of this medication?

A. ~~Increased estrogen effect on the pituitary~~ (1%)
B. ~~Inhibition of gonadotropin-releasing hormone secretion~~ (4%)
C. Inhibition of hypothalamic dopaminergic neurons (8%)
D. Stimulation of pituitary dopamine receptors (84%)
E. Stimulation of thyrotropin-releasing hormone receptors (1%)

Correct
84%
01 min, 16 secs
02/12/2021

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Explanation

Prolactinoma	
Clinical features	• **Premenopausal women**: Oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass-effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and are a common cause of

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Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, which directly stimulates milk secretion in the breasts. Pituitary lactotroph adenomas (**prolactinomas**) can cause very high prolactin levels and are a common cause of galactorrhea.

Unlike most pituitary hormones, which are under positive regulation by releasing hormones from the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of the tonic inhibitory effect of dopamine on prolactin secretion, **dopamine agonists** (eg, cabergoline, bromocriptine) can be used to treat hyperprolactinemia. Dopamine agonist therapy reduces adenoma size, suppresses prolactin production, and, in patients with small (<1 cm, as in this patient) prolactinomas and no mass-effect symptoms (eg, headache, visual field defects), can often induce a prolonged clinical response.

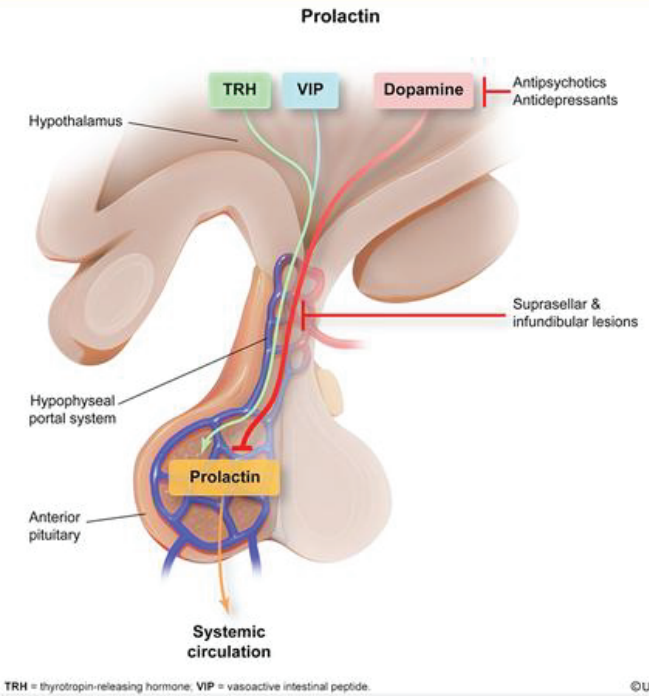
(Choices A and C) Estrogen stimulates prolactin gene transcription and secretion. Strongly estrogenic medications (eg, birth control pills) can potentially worsen rather than alleviate galactorrhea. Dopamine antagonists (eg, antipsychotics) directly increase prolactin secretion and also can worsen galactorrhea.

(Choice B) Hyperprolactinemia causes amenorrhea in women due to the inhibitory effect of prolactin on hypothalamic GnRH release. Dopaminergic medications suppress prolactin secretion and can restore

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(Choice B) Hyperprolactinemia causes amenorrhea in women due to the inhibitory effect of prolactin on hypothalamic GnRH release. Dopaminergic medications suppress prolactin secretion and can restore normal GnRH secretion.

(Choice E) Thyrotropin-releasing hormone (TRH) stimulates secretion of prolactin by lactotrophs, although its role in regulating prolactin release is secondary to the inhibition of prolactin secretion by dopamine. Factors that increase TRH release would worsen hyperprolactinemia.

Educational objective:
Galactorrhea is abnormal secretion of breast milk not associated with pregnancy or breastfeeding. It is most commonly due to excess prolactin, as seen in prolactin-secreting pituitary adenomas. Prolactin is under negative regulation by hypothalamic dopaminergic neurons, and dopamine agonists can be used to treat hyperprolactinemia.

References

- Evaluation and management of galactorrhea.

Pharmacology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

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A 32-year-old man is evaluated for recurrent nausea and vomiting. The patient has nausea and upper abdominal discomfort after meals and feels full even after eating a small amount of food. He also has experienced several episodes of vomiting of undigested food particles but has had no fever or diarrhea. The patient has a history of type 1 diabetes mellitus and diabetic neuropathy. Physical examination shows a clear oropharynx. The abdomen is soft, nondistended, and nontender with no organomegaly. Bowel sounds are normoactive. Stool testing for occult blood is negative. Upper gastrointestinal endoscopy reveals no abnormalities. Treatment with an oral medication is initiated, but it is stopped after the patient experiences abnormal involuntary movements. A macrolide antibiotic is prescribed, which improves his symptoms. Which of following mechanisms is most likely responsible for the improvement in this patient's symptoms?

A. Agonistic activity on motilin receptors
B. Blockade of gastrointestinal muscarinic receptors
C. Increase in intestinal fluid secretion
D. Protective effect on gastric mucosa
E. Suppression of intestinal bacterial growth

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abdominal discomfort after meals and feels full even after eating a small amount of food. He also has experienced several episodes of vomiting of undigested food particles but has had no fever or diarrhea. The patient has a history of type 1 diabetes mellitus and diabetic neuropathy. Physical examination shows a clear oropharynx. The abdomen is soft, nondistended, and nontender with no organomegaly. Bowel sounds are normoactive. Stool testing for occult blood is negative. Upper gastrointestinal endoscopy reveals no abnormalities. Treatment with an oral medication is initiated, but it is stopped after the patient experiences abnormal involuntary movements. A macrolide antibiotic is prescribed, which improves his symptoms. Which of following mechanisms is most likely responsible for the improvement in this patient's symptoms?

A. Agonistic activity on motilin receptors
B. Blockade of gastrointestinal muscarinic receptors
C. Increase in intestinal fluid secretion
D. Protective effect on gastric mucosa
E. Suppression of intestinal bacterial growth

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The patient has a history of type 1 diabetes mellitus and diabetic neuropathy. Physical examination shows a clear oropharynx. The abdomen is soft, nondistended, and nontender with no organomegaly. Bowel sounds are normoactive. Stool testing for occult blood is negative. Upper gastrointestinal endoscopy reveals no abnormalities. Treatment with an oral medication is initiated, but it is stopped after the patient experiences abnormal involuntary movements. A macrolide antibiotic is prescribed, which improves his symptoms. Which of following mechanisms is most likely responsible for the improvement in this patient's symptoms?

- A. Agonistic activity on motilin receptors (63%)
- B. ~~Blockade of gastrointestinal muscarinic receptors~~ (6%)
- C. ~~Increase in intestinal fluid secretion~~ (2%)
- D. ~~Protective effect on gastric mucosa~~ (3%)
- E. ~~Suppression of intestinal bacterial growth~~ (23%)

Correct

63%
Answered correctly

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This patient with diabetes mellitus has postprandial nausea, vomiting of undigested food, bloating, and early satiety, raising strong suspicion for **diabetic gastroparesis**, an autonomic neuropathy of the gastrointestinal tract marked by delayed gastric emptying in the absence of mechanical obstruction (eg, normal esophagogastroduodenoscopy [EGD]). Metoclopramide, a dopamine 2 receptor antagonist, can improve symptoms but is occasionally associated with extrapyramidal side effects (eg, dystonia) and tardive dyskinesia (eg, involuntary movements).

For patients with gastroparesis who cannot tolerate metoclopramide, **erythromycin**, a macrolide antibiotic, can be used as an alternate prokinetic agent. The prokinetic effects of erythromycin stem from the **activation of the motilin receptor** in the smooth muscle of the upper digestive tract, which results in coordinated peristaltic contractions that begin in the stomach and move through the entire upper digestive system (thereby propelling food into the colon).

When used as an antibiotic, erythromycin can cause significant abdominal cramping, but in the setting of gastroparesis, the prokinetic effects can be leveraged to improve gastric emptying and ameliorate gastroparesis symptoms. However, the agonist effects of erythromycin diminish over time (tachyphylaxis) so it is generally used for short periods (<4 weeks).

(Choices B and C) Patients with irritable bowel syndrome (IBS) who have significant gastrointestinal

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(Choices B and C) Patients with irritable bowel syndrome (IBS) who have significant gastrointestinal bloating symptoms can be treated with antispasmodic medications (eg, dicycloverine) that block gastrointestinal muscarinic receptors. Those with constipation-predominant IBS are sometimes treated with lubiprostone, a chloride channel activator, to increase intestinal fluid secretion. IBS is usually marked by periods of diarrhea and/or constipation and abdominal bloating; early satiety and vomiting of undigested food would be atypical.

(Choice D) Peptic ulcer disease (PUD) is treated with medications (eg, proton pump inhibitor, sucralfate) that have a protective effect on the gastrointestinal mucosa. Although PUD can occasionally cause nausea, vomiting, and early satiety due to gastric outlet obstruction, most patients have significant upper abdominal pain. In addition, an EGD would show a gastric or duodenal ulcer.

(Choice E) Patients with small intestinal bacterial overgrowth (SIBO)—colonization of the small intestine with colonic bacteria—often develop bloating, abdominal discomfort, flatulence, and/or diarrhea. However, early satiety and vomiting of undigested food would be atypical. In addition, SIBO is generally treated with rifaximin or neomycin.

Educational objective:
Erythromycin stimulates upper gastrointestinal motility by acting as an agonist on motilin receptors in the

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by periods of diarrhea and/or constipation and abdominal bloating; early satiety and vomiting of undigested food would be atypical.

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(Choice E) Patients with small intestinal bacterial overgrowth (SIBO)—colonization of the small intestine with colonic bacteria—often develop bloating, abdominal discomfort, flatulence, and/or diarrhea. However, early satiety and vomiting of undigested food would be atypical. In addition, SIBO is generally treated with rifaximin or neomycin.

Educational objective:
Erythromycin stimulates upper gastrointestinal motility by acting as an agonist on motilin receptors in the muscularis externa. Therefore, it can be used to treat gastroparesis (ie, delayed gastric emptying), a condition that frequently occurs in patients with long standing diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Gastroparesis
Subject	System	Topic

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A 19-year-old woman comes to the office for evaluation of amenorrhea. Onset of menarche was at age 12, and the patient then had menses regularly every 25-28 days. However, for the last year her menstrual periods have been irregular, and her last period was 3 months ago. The patient has no significant past medical history, eats mainly fruits and vegetables, and exercises regularly at a local gym. She does not use tobacco or alcohol. On further questioning, the patient expresses concern about being overweight and asks for suggestions on cutting down her caloric intake. On physical examination, BMI is 18 kg/m^2. The patient is thin and has dry skin covered by fine, downy hair. A pregnancy test is negative. Which of the following patterns of serum hormone levels is most likely in this patient?

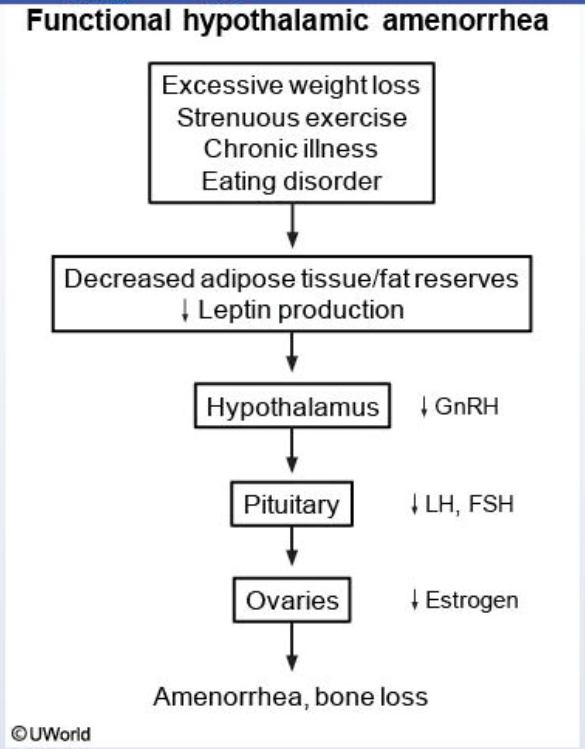
	LH	FSH	Estradiol
A.	Increased	Increased	Decreased
B.	Increased	Decreased	Decreased
C.	Decreased	Normal	Normal
D.	Decreased	Decreased	Decreased
E.	Normal	Normal	Decreased

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and the patient then had menses regularly every 25-28 days. However, for the last year her menstrual periods have been irregular, and her last period was 3 months ago. The patient has no significant past medical history, eats mainly fruits and vegetables, and exercises regularly at a local gym. She does not use tobacco or alcohol. On further questioning, the patient expresses concern about being overweight and asks for suggestions on cutting down her caloric intake. On physical examination, BMI is 18 kg/m^2. The patient is thin and has dry skin covered by fine, downy hair. A pregnancy test is negative. Which of the following patterns of serum hormone levels is most likely in this patient?

	LH	FSH	Estradiol	
A.	Increased	Increased	Decreased	(16%)
B.	Increased	Decreased	Decreased	(4%)
C.	Decreased	Normal	Normal	(2%)
✓ D.	Decreased	Decreased	Decreased	(74%)
E.	Normal	Normal	Decreased	(2%)

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Amenorrhea can be categorized as primary (failure of menarche by age 15) or secondary (cessation of menstruation in premenopausal women who have previously had menses). Secondary amenorrhea can be

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Amenorrhea can be categorized as primary (failure of menarche by age 15) or secondary (cessation of menstruation in premenopausal women who have previously had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient's distorted body image, restricted diet, exercise regimen, and physical examination findings (dry skin, lanugo hair) suggest anorexia nervosa with **functional hypothalamic amenorrhea** (FHA). The underlying pathophysiology of FHA appears to involve reduced circulating leptin levels as a result of diminished adipose tissue stores. The decrease in leptin inhibits pulsatile **gonadotropin-releasing hormone (GnRH)** release from the hypothalamus, causing decreased pituitary **LH and FSH** secretion, low circulating **estrogen** levels, and amenorrhea.

In addition to anorexia, FHA can also occur when caloric expenditure is out of proportion to intake, as in thin female athletes (eg, distance runners, dancers) or patients with chronic illness. Potential complications of FHA in young women include reduced peak bone mass, which may lead to early-onset osteoporosis.

Educational objective:
Distorted body image, inadequate diet, dry skin, and lanugo hair in a female suggest anorexia nervosa. Anorexic females commonly have impaired gonadotropin-releasing hormone release from the

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menstruation in premenopausal women who have previously had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient's distorted body image, restricted diet, exercise regimen, and physical examination findings (dry skin, lanugo hair) suggest anorexia nervosa with **functional hypothalamic amenorrhea** (FHA). The underlying pathophysiology of FHA appears to involve reduced circulating leptin levels as a result of diminished adipose tissue stores. The decrease in leptin inhibits pulsatile **gonadotropin-releasing hormone (GnRH)** release from the hypothalamus, causing decreased pituitary **LH and FSH** secretion, low circulating **estrogen** levels, and amenorrhea.

In addition to anorexia, FHA can also occur when caloric expenditure is out of proportion to intake, as in thin female athletes (eg, distance runners, dancers) or patients with chronic illness. Potential complications of FHA in young women include reduced peak bone mass, which may lead to early-onset osteoporosis.

Educational objective:
Distorted body image, inadequate diet, dry skin, and lanugo hair in a female suggest anorexia nervosa. Anorexic females commonly have impaired gonadotropin-releasing hormone release from the hypothalamus, leading to low levels of LH, FSH, and estrogen (functional hypothalamic amenorrhea).

References

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A 60-year-old woman comes to the office due to difficulty climbing stairs and dyspnea on exertion over the last 6 weeks. The patient has a 40-pack-year smoking history. Blood pressure is 160/90 mm Hg and pulse is 78/min. Auscultation of the chest reveals decreased breath sounds over the right lung base. Proximal muscle strength is 4 on a scale of 0-5. Skin examination shows scattered ecchymoses. Laboratory results show mild hyperglycemia and elevated 24-hour urinary free cortisol. Serum cortisol level is at the upper limit of normal and is not suppressed following administration of low-dose dexamethasone. Serum ACTH level is elevated. Chest x-ray reveals a right lower lobe lung mass. Which of the following changes are most likely to occur after administration of high-dose dexamethasone in this patient?

	ACTH	Cortisol
A.	Decrease	Decrease
B.	Increase	Increase
C.	Increase	No change
D.	No change	Decrease
E.	No change	No change

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is 78/min. Auscultation of the chest reveals decreased breath sounds over the right lung base. Proximal muscle strength is 4 on a scale of 0-5. Skin examination shows scattered ecchymoses. Laboratory results show mild hyperglycemia and elevated 24-hour urinary free cortisol. Serum cortisol level is at the upper limit of normal and is not suppressed following administration of low-dose dexamethasone. Serum ACTH level is elevated. Chest x-ray reveals a right lower lobe lung mass. Which of the following changes are most likely to occur after administration of high-dose dexamethasone in this patient?

	ACTH	Cortisol	
A.	Decrease	Decrease	(5%)
B.	Increase	Increase	(2%)
C.	Increase	No change	(1%)
D.	No change	Decrease	(8%)
✓ E.	No change	No change	(82%)

Correct

82%

01 min, 08 secs

10/21/2020

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Biochemical findings in Cushing syndrome			
Etiology	**ACTH**	**Cortisol**	**High-dose dexamethasone suppression test**
Pituitary adenoma	↑	↑	↓ Cortisol
Ectopic ACTH secretion	↑	↑	Cortisol remains elevated
Adrenal adenoma/carcinoma	↓	↑	

This patient's hypertension, proximal muscle weakness, and hyperglycemia are suggestive of excess cortisol (ie, **Cushing syndrome** [CS]). Hypercortisolism can be confirmed by finding elevated cortisol levels in a late-night salivary sample or 24-hour urine collection. Additionally, low-dose dexamethasone suppression testing can also be useful for confirming the diagnosis; administration of a small dose of a potent glucocorticoid rapidly suppresses ACTH and cortisol secretion in normal individuals, but patients with CS are resistant to low-dose glucocorticoids so serum cortisol remains elevated.

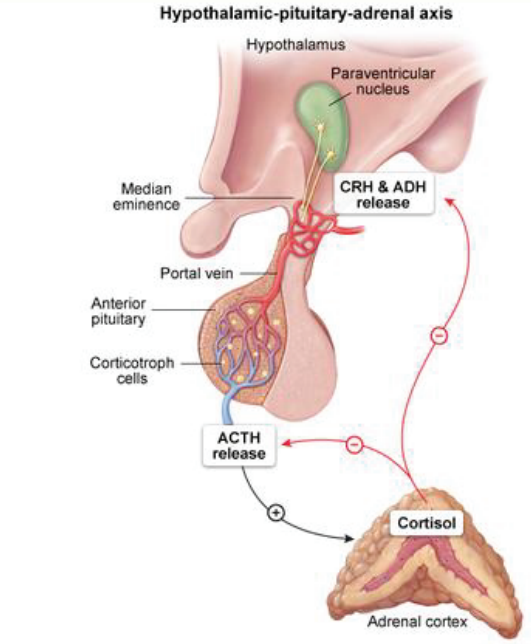
Once the diagnosis is confirmed, the next step is **establishing the cause** of CS, which involves measurement of serum ACTH levels:

- Low ACTH levels are seen with autonomous adrenal production of cortisol (eg, adrenal adenoma or

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This patient's hypertension, proximal muscle weakness, and hyperglycemia are suggestive of excess

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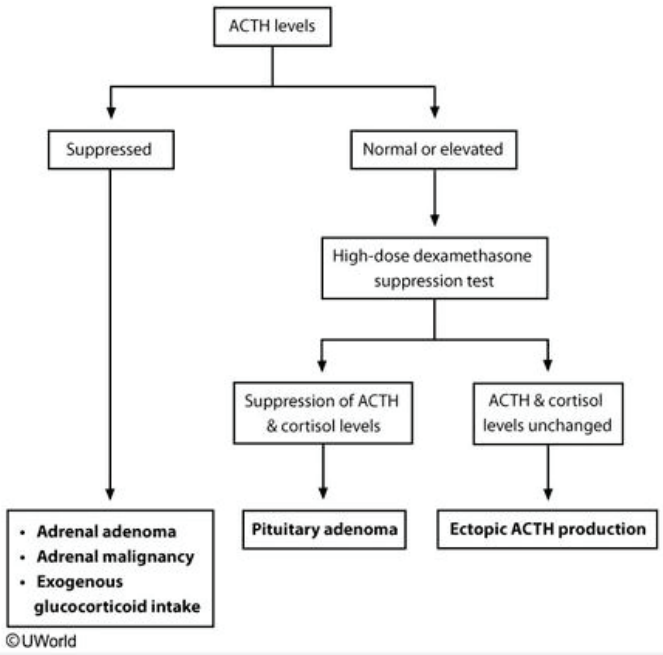
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This patient's hypertension, proximal muscle weakness, and hyperglycemia are suggestive of excess

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Diagnosing the cause of Cushing syndrome



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- Low ACTH levels are seen with autonomous adrenal production of cortisol (eg, adrenal adenoma or carcinoma) or exogenous glucocorticoid exposure due to feedback suppression
- **High ACTH** levels occur with pituitary adenomas (ie, Cushing disease) or ectopic ACTH production by nonpituitary tumors, which can be further distinguished with the **high-dose dexamethasone suppression test**:
  - Pituitary sources of ACTH are only relatively resistant to feedback inhibition, and high doses of dexamethasone will suppress ACTH and cortisol levels **(Choice A)**
  - Nonpituitary **ectopic sources** of ACTH (eg, **small cell lung cancer**) are completely resistant to feedback inhibition, and ACTH and cortisol will remain elevated following high doses of dexamethasone

This patient's rapid symptom onset, heavy smoking history, and lung mass are consistent with paraneoplastic CS, likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high-dose dexamethasone.

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In patients with abnormal pituitary or ectopic ACTH production, dexamethasone affects ACTH levels as described above. However, dexamethasone does not stimulate ACTH release in any setting.

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dexamethasone

This patient's rapid symptom onset, heavy smoking history, and lung mass are consistent with paraneoplastic CS, likely due to small cell lung cancer. **ACTH and cortisol production** will likely be **unchanged** following high-dose dexamethasone.

(Choices B and C) In normal individuals, dexamethasone suppresses ACTH release from the pituitary. In patients with abnormal pituitary or ectopic ACTH production, dexamethasone affects ACTH levels as described above. However, dexamethasone does not stimulate ACTH release in any setting.

(Choice D) The fall in cortisol seen in dexamethasone suppression tests is due to feedback suppression causing decreased ACTH release. A fall in cortisol would not be seen without a corresponding fall in ACTH.

Educational objective:
Cushing syndrome caused by a pituitary adenoma or ectopic (paraneoplastic) ACTH secretion is associated with elevated ACTH levels. High-dose dexamethasone suppresses ACTH and cortisol secretion when Cushing syndrome is caused by a pituitary adenoma (Cushing disease) but not when it is caused by ectopic ACTH secretion (eg, small cell lung cancer).

References

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A 19-year-old man is brought to the emergency department due to weakness and confusion. Family members report that for the last 2 weeks he has experienced polyuria, polydipsia, and increased appetite. Medical history is remarkable for an appendectomy at age 12. The patient does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in his brother. Temperature is 36.7 C (98 F), blood pressure is 90/60 mm Hg, pulse is 97/min, and respirations are 22/min. On physical examination, the patient is lethargic but follows simple commands. His breath has a fruity odor. This patient is most likely deficient in a hormone that normally performs which of the following actions?

A. Activates hormone-sensitive lipase
B. Decreases glucagon secretion
C. Decreases muscle glycogen synthesis
D. Increases hepatic glucose production
E. Increases renal glucose reabsorption

Submit

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A. Activates hormone-sensitive lipase (10%)
B. Decreases glucagon secretion (74%)
C. Decreases muscle glycogen synthesis (3%)
D. Increases hepatic glucose production (8%)
E. Increases renal glucose reabsorption (3%)

74%
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11/30/2020

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Insulin effects		
Effect	**Target organs**	**Consequences of inadequate insulin**
↑ Glucose uptake	• Skeletal muscle • Adipose tissue • Liver	• **Hyperglycemia** ◦ Polyuria, polydipsia ◦ Lethargy ◦ Polyphagia or anorexia
↑ Glycogen synthesis/ ↓ glycogenolysis	• Liver	
↓ Glucagon secretion	• Pancreas (alpha cells)	
↓ Lipolysis/ ↓ ketogenesis	• Adipose tissue • Liver	• Ketosis/ketoacidosis
↑ Protein synthesis	• Muscle	• Muscle wasting, weight loss

This patient has undiagnosed type 1 diabetes mellitus and is now presenting with **diabetic ketoacidosis** (polyuria, polydipsia, altered mental status, fruity breath [exhaled ketones]). Diabetic ketoacidosis results

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This patient has undiagnosed type 1 diabetes mellitus and is now presenting with **diabetic ketoacidosis** (polyuria, polydipsia, altered mental status, fruity breath [exhaled ketones]). Diabetic ketoacidosis results from a **deficiency of insulin** coupled with an excess of counterregulatory hormones (ie, glucagon, epinephrine).

Blood glucose levels are normally maintained within a tight range by the opposing effects of insulin (secreted by beta cells) and glucagon (secreted by alpha cells). In the fasting state, low blood glucose levels stimulate secretion of glucagon, which increases blood glucose levels by upregulating glycogenolysis and gluconeogenesis in the liver. In contrast, insulin is released in response to high glucose levels and functions to decrease hepatic glucose production **(Choice D)** and increase glucose uptake by insulin-responsive tissues. **Insulin** also **suppresses glucagon** by directly acting on the alpha cells, enhancing the metabolic effects of insulin.

In type 1 diabetes mellitus, unsuppressed glucagon secretion due to insulin deficiency contributes to excess blood glucose levels.

(Choice A) In adipose tissue, hormone-sensitive lipase hydrolyzes intracellular triglycerides to release free fatty acids. Hormone-sensitive lipase is activated by ACTH and epinephrine in the fasting state and is downregulated by insulin in the fed state. In untreated type 1 diabetes, the lack of insulin induces a

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(Choice A) In adipose tissue, hormone-sensitive lipase hydrolyzes intracellular triglycerides to release free fatty acids. Hormone-sensitive lipase is activated by ACTH and epinephrine in the fasting state and is downregulated by insulin in the fed state. In untreated type 1 diabetes, the lack of insulin induces a catabolic state, resulting in increased lipolysis; patients typically lose weight despite a normal or increased appetite.

(Choice C) In skeletal muscle, insulin increases glucose uptake and synthesis of glycogen, which is then available for energy production during exercise. Insulin also increases amino acid transport and ribosomal translation efficiency in muscle tissue, leading to an overall increase in protein synthesis. Insulin deficiency in type 1 diabetes leads to decreased muscle glycogen synthesis and muscle wasting.

(Choice E) In the renal tubules, glucose is actively taken up from the tubular lumen by sodium-glucose co-transporter 2 (SGLT2) and then passed across the basolateral membrane. This occurs independent of insulin levels and leads to near-complete reabsorption of filtered glucose (unless severe hyperglycemia overwhelms the reabsorptive capacity, leading to osmotic diuresis and polyuria).

Educational objective:
Normal blood glucose levels are maintained by the opposing effects of insulin and glucagon. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, whereas insulin increases peripheral glucose

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appetite.

(Choice C) In skeletal muscle, insulin increases glucose uptake and synthesis of glycogen, which is then available for energy production during exercise. Insulin also increases amino acid transport and ribosomal translation efficiency in muscle tissue, leading to an overall increase in protein synthesis. Insulin deficiency in type 1 diabetes leads to decreased muscle glycogen synthesis and muscle wasting.

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Educational objective:

Normal blood glucose levels are maintained by the opposing effects of insulin and glucagon. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, whereas insulin increases peripheral glucose uptake and inhibits lipolysis and ketoacid formation. Insulin also suppresses glucagon release.

References

- Minireview: glucagon in the pathogenesis of hypoglycemia and hyperglycemia in diabetes.

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A 50-year-old woman comes to the office concerned that her menstrual periods have stopped. She took oral contraceptive pills for the past 17 years, which she discontinued 3 months ago, and her menses have not returned. The patient had one spontaneous abortion at age 27 and otherwise has never been pregnant. She is monogamous with her husband, and they have sexual intercourse regularly. The patient has some vaginal dryness but no pain or discomfort with intercourse. BMI is 21 kg/m^2 and vital signs are normal. Speculum examination shows a normal vaginal mucosa and cervix. Bimanual examination shows a normal uterus and ovaries. Urine pregnancy test is negative. Which of the following hormones is most likely elevated in this patient?

A. β-hCG
B. Estradiol
C. FSH
D. Progesterone
E. Prolactin

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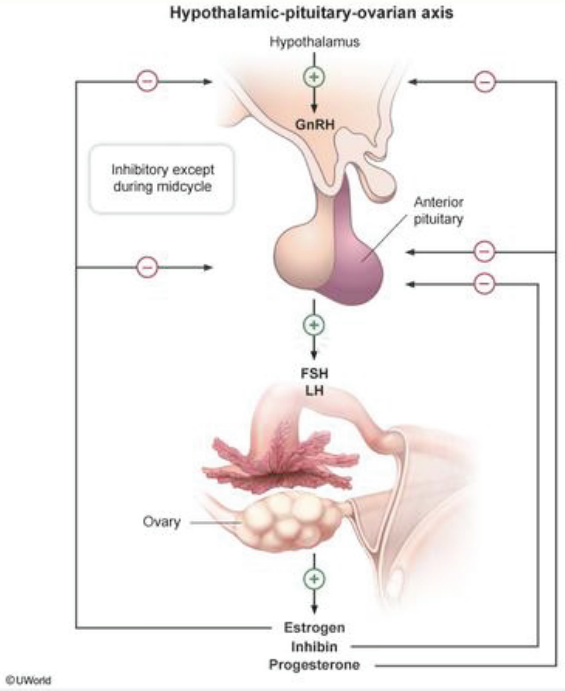
A. β-hCG (0%)
B. Estradiol (5%)
✓ C. FSH (74%)
D. Progesterone (11%)
E. Prolactin (7%)

Correct
74%
40 secs
11/08/2020

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Menopause is defined by the permanent cessation of menses for **12 months** and is a normal event of aging caused by exhaustion of ovarian follicles. The mean age of menopause in the United States is 51. Ovarian failure before age 35 is considered premature. During the menopausal transition, **FSH levels increase** due to resistant ovarian follicles and lack of feedback from inhibin. Absence of menstrual cycles with associated **hypoestrogenic symptoms** (eg, hot flashes, vaginal dryness) is highly suggestive of menopause. Menopause is typically diagnosed clinically. However, if the diagnosis is unclear, an elevated serum FSH level can be used for diagnosis as it is a reliable early indicator.

Cyclic and continuous oral contraceptive (OC) regimens are not associated with irregular menses or amenorrhea, and premenopausal patients who stop taking OCs should expect spontaneous return of menses. This patient's age and vaginal dryness make menopausal transition the most likely cause of amenorrhea. OCs may mask vasomotor symptoms that are typical of menopausal transition, and the patient was likely having iatrogenic withdrawal bleeding.

(Choice A) A urine pregnancy test should be performed for any female of reproductive age with amenorrhea. A negative test is a reliable indicator that the patient is not pregnant. Serum β-hCG testing is indicated in cases when the absolute value of the β-hCG would aid in diagnosis and treatment, such as in ectopic or molar pregnancies.

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patient was likely having iatrogenic withdrawal bleeding.

(Choice A) A urine pregnancy test should be performed for any female of reproductive age with amenorrhea. A negative test is a reliable indicator that the patient is not pregnant. Serum β-hCG testing is indicated in cases when the absolute value of the β-hCG would aid in diagnosis and treatment, such as in ectopic or molar pregnancies.

(Choices B and D) Estradiol and progesterone levels gradually decrease during the menopausal transition due to decreasing ovarian function. Serum estradiol measurement is not a reliable indicator of menopause due to typical fluctuations and gradual decline. After menopause, estrone is produced outside the ovaries and replaces estradiol as the predominant circulating estrogen.

(Choice E) Serum prolactin levels are much less significantly changed during menopause than are FSH levels. Amenorrhea due to a prolactinoma would be diagnosed by detecting an elevated prolactin level. Additional symptoms can include galactorrhea and headache, which this patient does not have.

Educational objective:

Menopause occurs on average at age 51 and is diagnosable retrospectively after 12 months of amenorrhea. An elevated serum FSH level confirms the diagnosis.

References

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A 34-year-old man comes to the office for a follow-up visit. The patient has had type 1 diabetes since age 12 and is diligent in taking insulin to achieve good glycemic control. Over the past few months, he has had more frequent episodes of hypoglycemia despite no changes in his treatment, diet, or physical activity, but the episodes have been associated with less severe hypoglycemic symptoms compared to prior episodes. Physical examination is unremarkable. Laboratory results show normal basic metabolic panel and serum TSH level. Hemoglobin A1c is 7.0%. Which of the following factors is primarily responsible for this patient's increased frequency of hypoglycemia?

A. Decreased epinephrine release
B. Decreased glucagon release
C. Decreased growth hormone release
D. Downregulation of insulin receptors
E. Upregulation of beta-adrenergic receptors

Submit

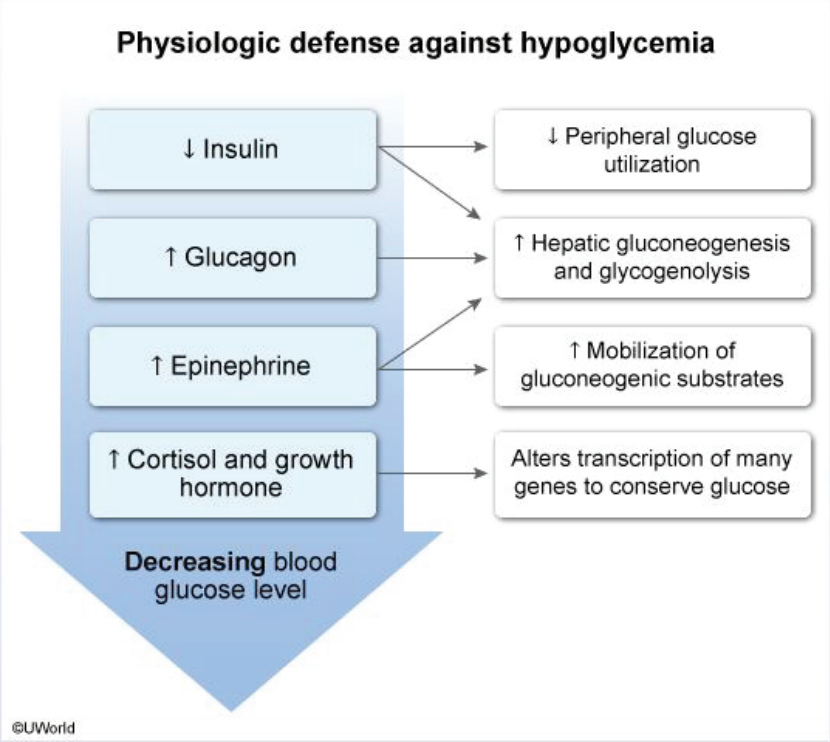
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A. ~~Decreased epinephrine release~~ (9%)
✓ B. Decreased glucagon release (38%)
C. ~~Decreased growth hormone release~~ (12%)
D. ~~Downregulation of insulin receptors~~ (19%)
E. Upregulation of beta-adrenergic receptors (20%)

38% 01 min, 22 secs 11/23/2020

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As blood glucose levels fall through the physiologic range, insulin secretion by pancreatic beta cells

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As blood glucose levels fall through the physiologic range, insulin secretion by pancreatic beta cells decreases, leading to reduced peripheral uptake and utilization of glucose. At the same time, alpha cells increase secretion of **glucagon**, which is the **primary counterregulatory hormone** to insulin and acts on the liver to rapidly increase glycogenolysis and gluconeogenesis and decrease glycolysis.

Patients with **type 1 diabetes mellitus** are at increased **risk of hypoglycemia** because **exogenous insulin** is not subject to the same regulation as endogenous insulin and will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes (ie, >5 years) frequently also have **alpha cell failure** with **decreased glucagon secretion** and therefore have an even greater risk of rapid hypoglycemia. Patients with pancreatogenic diabetes (eg, secondary to chronic pancreatitis) also typically have inadequate alpha cell reserve and can experience frequent hypoglycemia.

(Choice A) Progressive hypoglycemia prompts a catecholamine (eg, epinephrine) surge, which increases hepatic glucose production and triggers many of the characteristic hypoglycemic symptoms (eg, arousal, tremor). Patients with long-standing diabetes often have a blunted autonomic response to hypoglycemia, with **reduced hypoglycemic awareness**, but catecholamines are less important than glucagon in raising blood glucose levels.

(Choice C) Prolonged hypoglycemia can stimulate secretion of cortisol and growth hormone, which

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tremor). Patients with long-standing diabetes often have a blunted autonomic response to hypoglycemia, with **reduced hypoglycemic awareness**, but catecholamines are less important than glucagon in raising blood glucose levels.

(Choice C) Prolonged hypoglycemia can stimulate secretion of cortisol and growth hormone, which increase glucose levels. These hormones typically act over longer timescales (eg, days/weeks) and are less important than glucagon in preventing acute hypoglycemia.

(Choice D) Chronic exposure to high circulating insulin levels leads to downregulation of insulin receptors and reduced insulin sensitivity. This effect promotes hyperglycemia, not hypoglycemia.

(Choice E) Repeated hypoglycemia causes downregulation of beta-adrenergic receptors, which contributes to reduced hypoglycemic awareness. Depending on the systems involved, upregulation of beta-adrenergic receptors would generally reduce hypoglycemia and increase awareness.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk of hypoglycemia because exogenous insulin will continue to be absorbed from the injection site despite falling glucose levels. Those with long-standing diabetes may also have decreased glucagon secretion and therefore have an even greater risk of rapid hypoglycemia.

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A 34-year-old woman comes to the office with progressive weight gain over the past year. She also has weakness, easy bruising, and irregular menstrual periods. The patient takes no medications and has no drug allergies. Blood pressure is 150/90 mm Hg and pulse is 78/min. Laboratory studies reveal an elevated serum cortisol level that is not suppressed following administration of low-dose dexamethasone. Her 24-hour urine free-cortisol concentration and plasma ACTH are elevated. Which of the following histopathologic findings are most likely to be present in this patient's adrenal glands?

A. Adenoma of the zona glomerulosa
B. Atrophy of all layers of the adrenal cortex
C. Hyperplasia of the adrenal medulla
D. Hyperplasia of the zona fasciculata and reticularis
E. Neoplasia of adrenal medulla

Submit

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A. ~~Adenoma of the zona glomerulosa~~ (6%)
B. Atrophy of all layers of the adrenal cortex (8%)
C. Hyperplasia of the adrenal medulla (3%)
✓ D. Hyperplasia of the zona fasciculata and reticularis (80%)
E. Neoplasia of adrenal medulla (1%)

Correct

80%
Answered correctly

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Common causes of Cushing syndrome		
	Etiology	**Pathologic findings**
ACTH-dependent	Cushing disease (ie, pituitary ACTH hypersecretion)	• Bilateral hyperplasia involving the zona fasciculata & reticularis
	Ectopic ACTH syndrome (eg, paraneoplastic ACTH secretion)	
ACTH-independent	Adrenal adenoma or carcinoma	• Benign tumors are typically round, well-circumscribed lesions with cells similar to normal zona fasciculata • Malignant tumors are often irregular and poorly demarcated with considerable cellular pleomorphism • Atrophy of the zona fasciculata & reticularis in the uninvolved cortex regions

This patient has symptoms of hypercortisolism, including weight gain, weakness, and easy bruising. She

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This patient has symptoms of hypercortisolism, including weight gain, weakness, and easy bruising. She also has increased 24-hour urine excretion of cortisol and an elevated serum cortisol level that is not suppressed by low-dose dexamethasone, which confirm the diagnosis of Cushing syndrome. In addition, her ACTH level is elevated (ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and induce cellular proliferation (**hyperplasia**).

(Choice A) Although increased ACTH can have a transient effect on aldosterone production, angiotensin II is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids (primary hyperaldosteronism [Conn syndrome]), which presents with hypertension and hypokalemia (muscle weakness).

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Features of Cushing syndrome Features of Cushing syndrome

Features of Cushing syndrome	
Clinical manifestations	• **Central obesity** • Skin atrophy & wide, purplish **striae** • Proximal muscle weakness • Hypertension • **Glucose intolerance** • Skin hyperpigmentation (if due to ACTH excess) • Depression, anxiety
Diagnosis	• 24-hour urinary cortisol excretion • Late-night salivary cortisol assay • Low-dose dexamethasone suppression test

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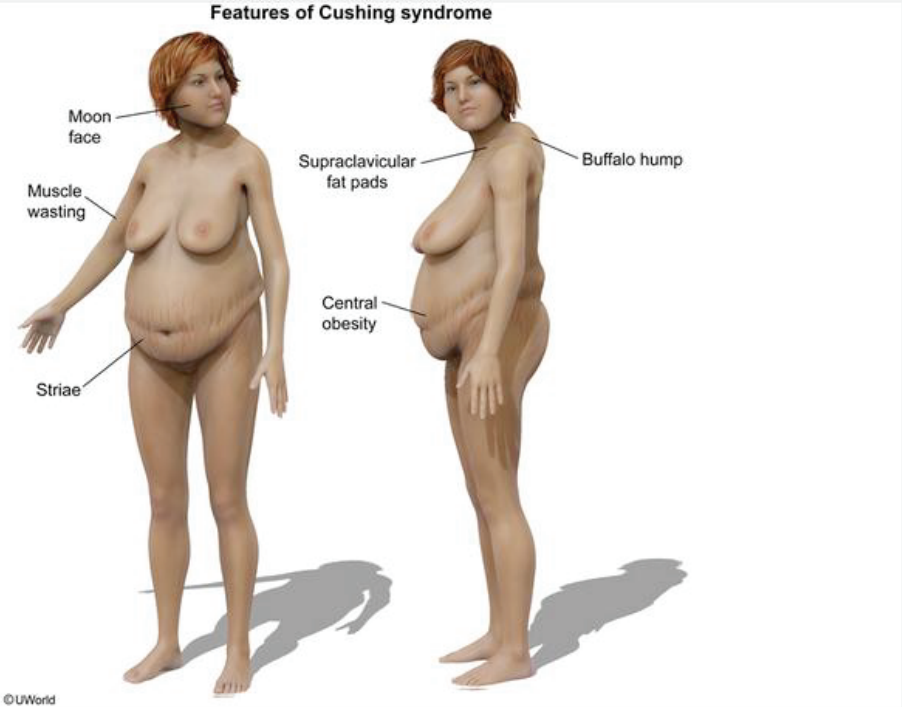
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Features of Cushing syndrome Features of Cushing syndrome



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is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids (primary hyperaldosteronism [Conn syndrome]), which presents with hypertension and hypokalemia (muscle weakness).

(Choice B) Atrophy of the entire adrenal cortex is most commonly caused by autoimmune adrenalitis and presents with chronic adrenal insufficiency (Addison disease). There is a compensatory rise in ACTH secretion, but, unlike in this patient, urine cortisol excretion is not elevated.

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of the adrenal medulla. Adrenal medullary hyperplasia is a rare disorder that may be a precursor to pheochromocytoma. These disorders typically present with symptoms of catecholamine excess (eg, palpitations, diaphoresis) and episodic hypertension. Patients have elevated blood and urine levels of catecholamines rather than cortisol.

Educational objective:
ACTH is the major trophic hormone of the zona fasciculata and reticularis, whereas the zona glomerulosa is primarily regulated by angiotensin II. Excess production of ACTH causes increased cortisol synthesis within the zona fasciculata (Cushing's manifestations) and increased androgen production within the zona reticularis (irregular menstruation, hirsutism in women).

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A 35-year-old woman comes to the emergency department due to a "racing heart" and shortness of breath. She has had insomnia and increasing anxiety for the past several weeks. The patient has no prior medical problems and takes no medications. She has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg and pulse is 120/min. Physical examination shows a diffusely enlarged, warm thyroid gland. There is a fine tremor in her outstretched hands. ECG shows sinus tachycardia. Serum TSH is decreased and free thyroxine (T4) is increased. The patient is treated with multiple drugs, including propranolol. In addition to its beta-adrenergic receptor-blocking activity, this drug is likely to decrease which of the following?

A. Binding of triiodothyronine (T3) to its receptors
B. New thyroid hormone synthesis
C. Peripheral conversion of T4 to T3
D. Release of T4 by the thyroid gland
E. Serum levels of TSH receptor antibodies

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A. Binding of triiodothyronine (T3) to its receptors (11%)
B. New thyroid hormone synthesis (7%)
C. Peripheral conversion of T4 to T3 (69%)
D. Release of T4 by the thyroid gland (9%)
E. Serum levels of TSH receptor antibodies (1%)

Correct

69%
Answered correctly

46 secs
Time Spent

09/06/2020
Last Updated

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T3 = triiodothyronine; T4 = thyroxine.

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This patient has primary **hyperthyroidism** with an elevated thyroxine (T4) and suppressed TSH level. In light of her diffuse goiter, this is likely due to Graves disease. Hyperthyroidism causes **upregulation of beta-adrenergic receptor expression**, leading to **increased catecholamine effect** manifesting as hypertension, palpitations/tachycardia, heat intolerance, tremor, and hyperreflexia.

Beta blockers (eg, propranolol) are used to **blunt the adrenergic manifestations** of hyperthyroidism while awaiting definitive management (eg, surgery, radioiodine). In addition, lipid-soluble beta blockers (including propranolol) **reduce conversion of T4 to triiodothyronine (T3)**, the more active form of thyroid hormone, by inhibiting 5'-monodeiodinase in peripheral tissues. Peripheral conversion of T4 to T3 is also decreased by glucocorticoids and propylthiouracil.

(Choice A) The thyroid hormone receptor functions as a transcriptional modulator of several thyroid hormone–responsive genes. It is an intranuclear protein, and binding is not affected by beta blockers.

(Choices B and D) Thionamides (eg, propylthiouracil, methimazole) decrease thyroid hormone synthesis by inhibiting thyroid peroxidase. Iodine inhibits release of T4 and T3 from the thyroid. However, beta blockers do not alter thyroid hormone synthesis or release.

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hormone–responsive genes. It is an intranuclear protein, and binding is not affected by beta blockers.

(Choices B and D) Thionamides (eg, propylthiouracil, methimazole) decrease thyroid hormone synthesis by inhibiting thyroid peroxidase. Iodine inhibits release of T4 and T3 from the thyroid. However, beta blockers do not alter thyroid hormone synthesis or release.

(Choice E) Graves disease is caused by autoantibodies that bind and stimulate the TSH receptor. Glucocorticoids and other immunosuppressive agents can decrease production of these antibodies, but beta blockers do not affect serum levels of TSH receptor antibodies.

Educational objective:

Hyperthyroidism causes upregulation of beta-adrenergic receptor expression, leading to increased catecholamine effect. Beta blockers are used to blunt the adrenergic manifestations of hyperthyroidism. In addition, lipid-soluble beta blockers reduce conversion of T4 to T3 by inhibiting 5'-monodeiodinase in peripheral tissues.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 62-year-old woman is brought to the emergency department after a fall and is found to have a left femoral neck fracture. The patient is admitted to the hospital, and a hip arthroplasty is planned. Medical history is significant for long-standing type 2 diabetes mellitus, hypertension, hyperlipidemia, and migraines. While hospitalized, the patient receives a combination of long- and short-acting insulin for diabetes management. On the morning of surgery, fasting blood glucose level is 42 mg/dL. The patient is awake and alert and says she feels hungry but has no other symptoms of hypoglycemia. Concurrent use of which of the following medications best explains this finding?

A. Atorvastatin
B. Doxazosin
C. Hydrochlorothiazide
D. Losartan
E. Propranolol
F. Verapamil

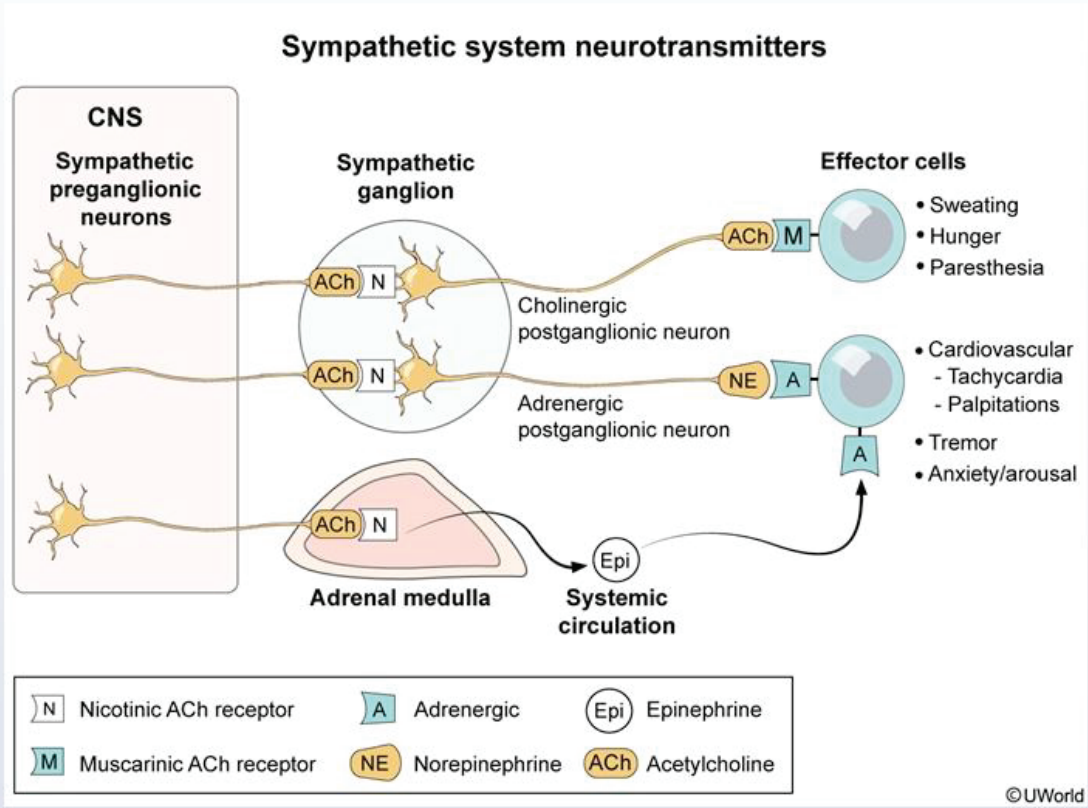
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femoral neck fracture. The patient is admitted to the hospital, and a hip arthroplasty is planned. Medical history is significant for long-standing type 2 diabetes mellitus, hypertension, hyperlipidemia, and migraines. While hospitalized, the patient receives a combination of long- and short-acting insulin for diabetes management. On the morning of surgery, fasting blood glucose level is 42 mg/dL. The patient is awake and alert and says she feels hungry but has no other symptoms of hypoglycemia. Concurrent use of which of the following medications best explains this finding?

A. Atorvastatin (6%)
B. Doxazosin (6%)
C. Hydrochlorothiazide (16%)
D. Losartan (4%)
E. Propranolol (63%)
F. Verapamil (2%)

Correct
63%
51 secs
12/05/2020

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Prolonged hypoglycemia can lead to irreversible neurologic deficits and death. To prevent injury, counterregulatory systems raise blood glucose in response to hypoglycemia via sympathetic nervous system activation (ie, norepinephrine/**epinephrine** release) and increase secretion of **glucagon**, cortisol, and growth hormone.

Symptoms of hypoglycemia fall into 2 general categories: neurogenic (autonomic) and neuroglycopenic.

- **Neurogenic symptoms** are mediated via norepinephrine/epinephrine and acetylcholine release during sympathetic stimulation. Symptoms due to **norepinephrine/epinephrine** include tremulousness, tachycardia, and anxiety/arousal, whereas **acetylcholine** causes sweating, hunger, and paresthesias.
- **Neuroglycopenic symptoms** are due to inadequate availability of glucose in the CNS and include behavioral changes, confusion, visual disturbances, stupor, and seizures.

This patient has **reduced awareness** of hypoglycemia, likely due to the use of a **nonselective beta blocker** (eg, propranolol) for chronic treatment of migraines and/or hypertension. Nonselective beta blockers attenuate the norepinephrine/epinephrine-mediated symptoms of hypoglycemia, but cholinergic symptoms (eg, hunger) are unaffected. In addition, nonselective beta blockers can contribute to the severity of hypoglycemia: epinephrine stimulates hepatic gluconeogenesis and peripheral glycogenolysis

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blockers attenuate the norepinephrine/epinephrine-mediated symptoms of hypoglycemia, but cholinergic symptoms (eg, hunger) are unaffected. In addition, nonselective beta blockers can contribute to the severity of hypoglycemia; epinephrine stimulates hepatic gluconeogenesis and peripheral glycogenolysis, but this effect is diminished by nonselective beta blockers.

(Choices A and C) Statins (eg, atorvastatin) and hydrochlorothiazide can increase blood glucose levels but would not mask symptoms of hypoglycemia.

(Choice B) Insulin-secreting pancreatic beta cells have alpha-2 and beta-2 receptors; stimulation of alpha-2 receptors inhibits insulin secretion, whereas stimulation of beta-2 receptors increases insulin secretion. Doxazosin is a selective alpha-1 blocker and has no effect on glucose levels.

(Choices D and F) Angiotensin II receptor blockers (eg, losartan) and nondihydropyridine calcium channel blockers (eg, verapamil) do not mask the symptoms of hypoglycemia and have virtually no effect on glucose levels.

Educational objective:
Nonselective beta blockers exacerbate hypoglycemia and mask hypoglycemic symptoms mediated by norepinephrine/epinephrine.

References

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A 45-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 3 years ago after developing polyuria, polydipsia, and recurrent vulvovaginal candidiasis. She initially tried lifestyle changes but had no significant glycemic improvement and was started on metformin. The patient is adherent with her therapy and consumes a low-carbohydrate diet. Family history is significant for an osteoporotic fracture in her mother. Blood pressure is 134/86 mm Hg and pulse is 72/min. BMI is 33 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 8.2%. After further discussion, a sodium-glucose cotransporter-2 inhibitor is added to the patient's drug regimen. Which of the following is the most likely additional effect of the newly prescribed medication?

A. Decreased blood pressure
B. Decreased genitourinary infections
C. Increased bone mineral density
D. Increased fluid retention
E. Increased postprandial satiety

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candidiasis. She initially tried lifestyle changes but had no significant glycemic improvement and was started on metformin. The patient is adherent with her therapy and consumes a low-carbohydrate diet. Family history is significant for an osteoporotic fracture in her mother. Blood pressure is 134/86 mm Hg and pulse is 72/min. BMI is 33 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 8.2%. After further discussion, a sodium-glucose cotransporter-2 inhibitor is added to the patient's drug regimen. Which of the following is the most likely additional effect of the newly prescribed medication?

A. Decreased blood pressure (73%)
B. ~~Decreased genitourinary infections~~ (4%)
C. ~~Increased bone mineral density~~ (2%)
D. Increased fluid retention (11%)
E. ~~Increased postprandial satiety~~ (8%)

Incorrect
Correct answer

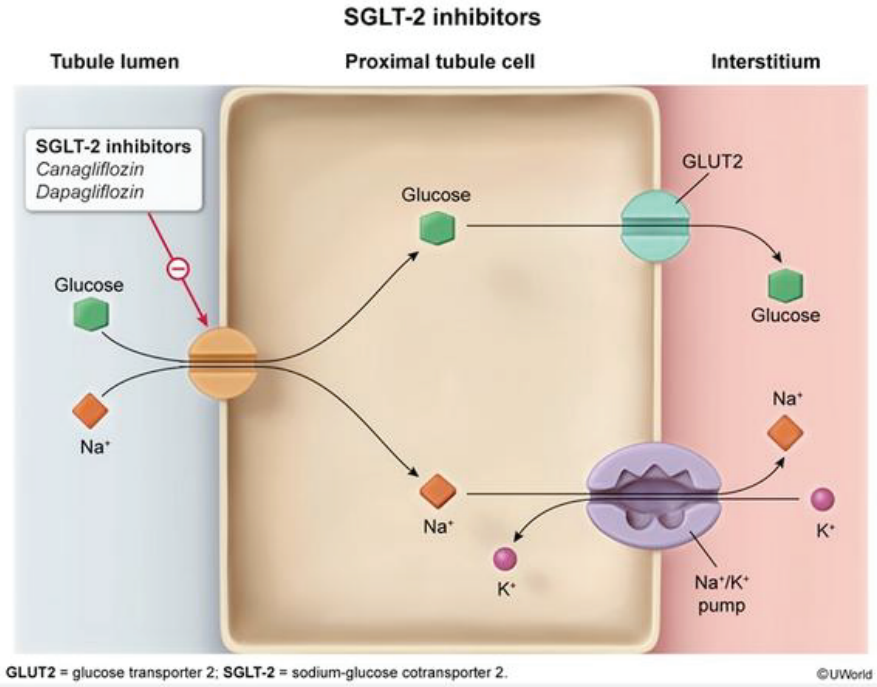
73%

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11/29/2020

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Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal renal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose and sodium**.

By decreasing glucose reabsorption, SGLT2 inhibitors **lower blood glucose levels**. Because the effect of SGLT2 inhibitors is dependent on the filtered glucose load, and because they do not stimulate insulin production, these medications are associated with a low risk of hypoglycemia. Patients may also experience weight loss due to glucose loss in the urine.

In addition, the decreased reabsorption of sodium and glucose induces **osmotic diuresis**, which causes a small **decrease in blood pressure**. This effect is associated with a decreased risk for cardiovascular events and a lower rate of hospitalization for heart failure. However, the resulting hypovolemia can lead to **orthostatic hypotension** in some patients and may increase the risk for acute kidney injury.

(Choice B) Due to the excess urinary glucose content, SGLT2 inhibitors are associated with an increased risk of genitourinary tract infections (eg, vaginitis, Fournier's gangrene).

(Choice C) Decreased sodium resorption can lead to increased phosphate reabsorption in the distal tubule, which can stimulate secretion of parathyroid hormone and lead to decreased bone density.

(Choice D) Thiazolidinediones (eg, pioglitazone) are antidiabetic medications that are associated with fluid

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risk of genitourinary tract infections (eg, vaginitis, Fournier's gangrene).

(Choice C) Decreased sodium resorption can lead to increased phosphate reabsorption in the distal tubule, which can stimulate secretion of parathyroid hormone and lead to decreased bone density.

(Choice D) Thiazolidinediones (eg, pioglitazone) are antidiabetic medications that are associated with fluid retention, but the SGLT2 inhibitors induce net loss of fluid and sodium.

(Choice E) Glucagon-like polypeptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing glucose-dependent insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) are parenteral agents used for management of type 2 diabetes that increase postprandial satiety and induce weight loss.

Educational objective:
Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose and sodium, leading to lower blood glucose levels. The decreased reabsorption of sodium and glucose also induces osmotic diuresis, which causes a decrease in blood pressure. Excess urinary glucose also leads to an increased risk for genitourinary tract infections.

References

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A 25-year-old woman comes to the office because of jitteriness, frequent mood swings, and palpitations for the past 2 months. At times, her symptoms make her worry that she may be having a heart attack. The patient has no prior medical conditions. Temperature is 37 C (98.6 F), blood pressure is 120/82 mm Hg, pulse is 102/min, and respirations are 12/min. Examination shows warm, moist skin and a fine tremor of the fingers. Which of the following would most likely provide the fastest relief of this patient's symptoms?

- A. Fluoxetine
- B. Methimazole
- C. Prazosin
- D. Propranolol
- E. Radioactive iodine

Submit

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A 25-year-old woman comes to the office because of jitteriness, frequent mood swings, and palpitations for the past 2 months. At times, her symptoms make her worry that she may be having a heart attack. The patient has no prior medical conditions. Temperature is 37 C (98.6 F), blood pressure is 120/82 mm Hg, pulse is 102/min, and respirations are 12/min. Examination shows warm, moist skin and a fine tremor of the fingers. Which of the following would most likely provide the fastest relief of this patient's symptoms?

- A. Fluoxetine (3%)
- B. Methimazole (8%)
- C. Prazosin (1%)
- ✓ D. Propranolol (83%)
- E. Radioactive iodine (3%)

Correct

83%
Answered correctly

01 min, 06 secs
Time Spent

01/19/2021
Last Updated

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General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

This patient has signs and symptoms of **thyrotoxicosis**, including tremor, dysphoria, sweating, and

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This patient has signs and symptoms of **thyrotoxicosis**, including tremor, dysphoria, sweating, and tachycardia with palpitations. Hyperthyroidism is associated with **upregulation of beta-adrenergic receptors** and increased adrenergic tone, which is responsible for many of the associated clinical features.

Beta-adrenergic antagonists (eg, propranolol) are indicated to **alleviate the adrenergic symptoms** of thyrotoxicosis and are usually prescribed early, while completing the diagnostic evaluation and initiating definitive management (eg, antithyroid medication, radioiodine ablation, thyroidectomy). Some beta-adrenergic antagonists (eg, propranolol) also reduce peripheral conversion of thyroxine (T4) to triiodothyronine (T3), although this effect is delayed.

(Choice A) Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used to treat anxiety or depression. This patient's anxiety and mood symptoms will likely resolve with treatment of the underlying condition (ie, thyrotoxicosis). Also, SSRIs typically require 2-4 weeks for a noticeable effect.

(Choice B) Thioamides (eg, methimazole, propylthiouracil) reduce the production of thyroid hormone by inhibiting thyroperoxidase, the enzyme responsible for iodination of tyrosine residues in follicular colloid. Although these agents are indicated for the treatment of hyperthyroidism due to overproduction of thyroid hormone (eg, Graves disease), they produce clinical effects only after a few weeks.

(Choice C) Prazosin is an alpha-1 adrenergic antagonist. Alpha-1 adrenergic receptors are present on the

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(Choice B) Thioamides (eg, methimazole, propylthiouracil) reduce the production of thyroid hormone by inhibiting thyroperoxidase, the enzyme responsible for iodination of tyrosine residues in follicular colloid. Although these agents are indicated for the treatment of hyperthyroidism due to overproduction of thyroid hormone (eg, Graves disease), they produce clinical effects only after a few weeks.

(Choice C) Prazosin is an alpha-1 adrenergic antagonist. Alpha-1 adrenergic receptors are present on the vasculature and induce vasoconstriction when stimulated. Blockade of these receptors would not alleviate the patient's palpitations and tremor.

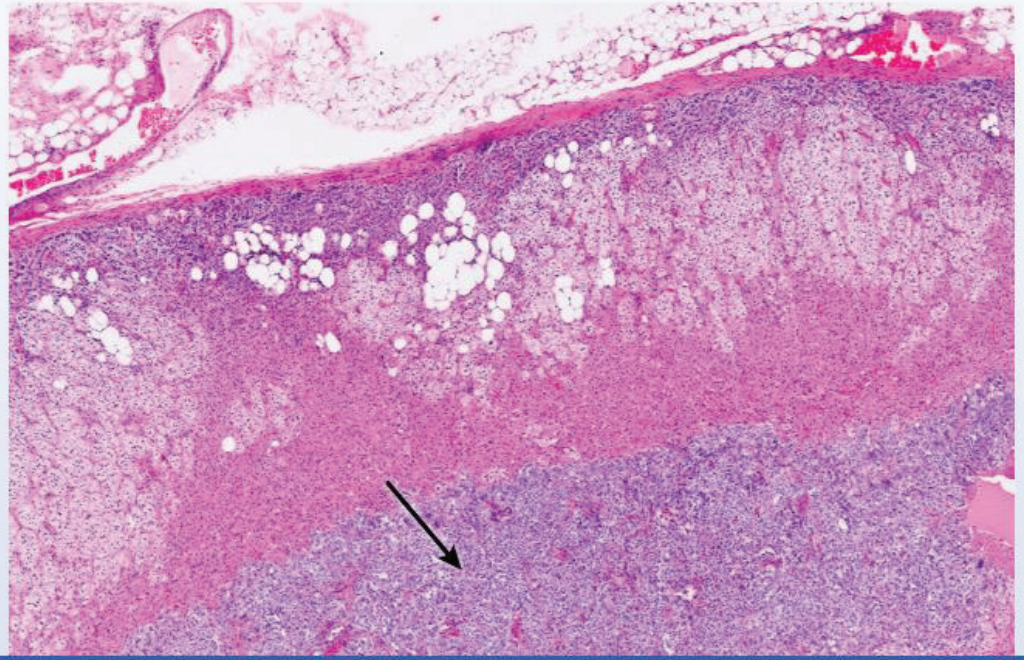
(Choice E) Radioactive iodine is used to treat a variety of hyperthyroid disorders, most commonly Graves disease, but it takes several weeks to be effective. In addition, it occasionally causes a paradoxical increase in thyroid hormone production early in treatment (jod-Basedow effect) and therefore should be administered with beta-adrenergic antagonists.

Educational objective:
Beta blockers provide rapid relief of the adrenergic-mediated symptoms of thyrotoxicosis and can be given while awaiting diagnostic evaluation and definitive management.

Pharmacology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

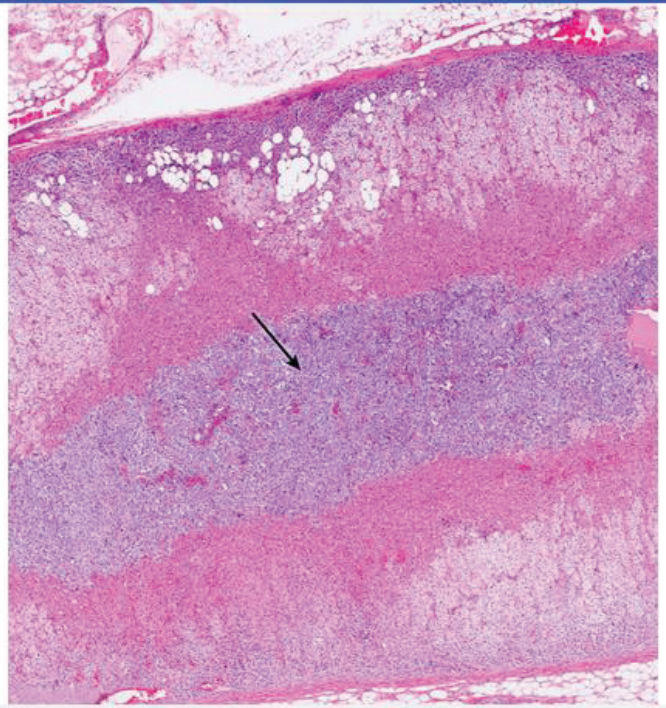
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A researcher is investigating factors affecting adrenal hormone synthesis and release. An intact adrenal gland is obtained from a donor cadaver, and a histologic section through the entire gland is shown below. Cells from a specific part of the gland, indicated by the arrow, are extracted for further analysis.



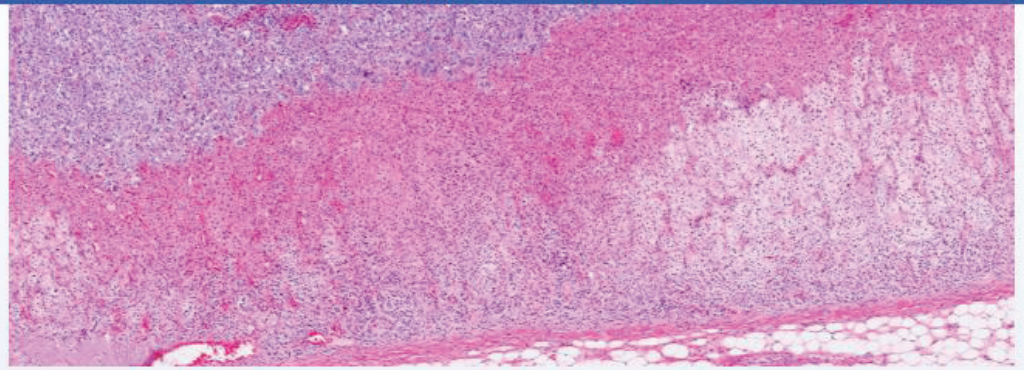
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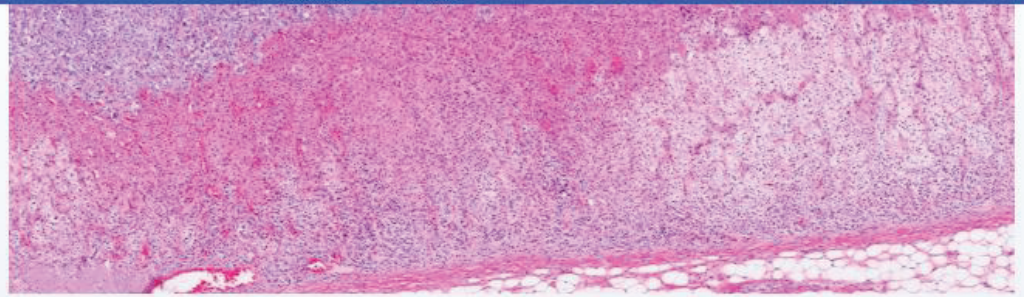
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These cells are most likely to be directly activated by which of the following substances?

A. Acetylcholine
B. ACTH
C. Angiotensin II
D. Epinephrine
E. Norepinephrine

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These cells are most likely to be directly activated by which of the following substances?

- A. Acetylcholine (41%)
- B. ACTH (39%)
- C. Angiotensin II (6%)
- D. Epinephrine (7%)
- E. Norepinephrine (6%)

Incorrect
Correct answer

41%

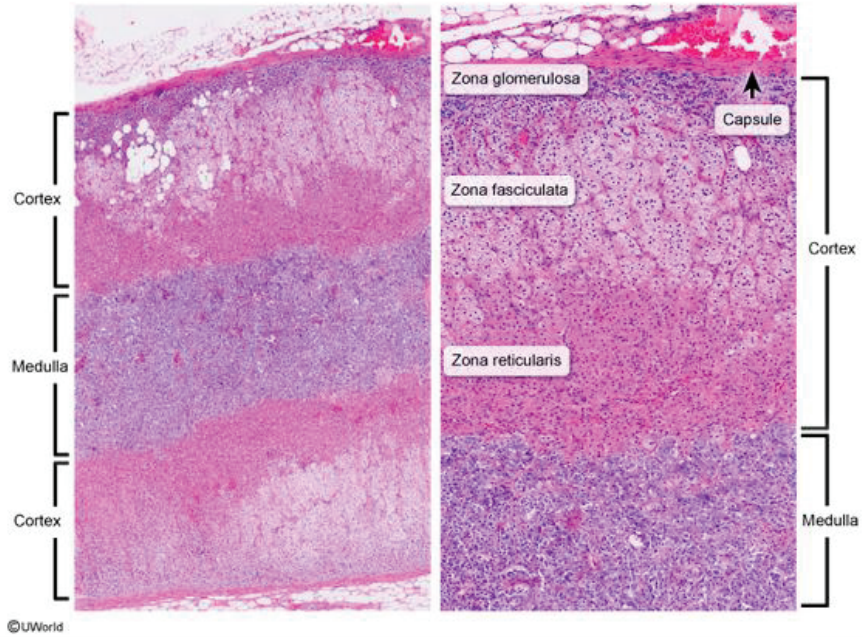
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Normal adrenal gland



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The adrenal gland is made up of an outer cortex (divided into 3 zones) and an inner medulla:

1. The zona glomerulosa is the outermost zone of the cortex and is composed of cells arranged in rounded or arched clusters (*glomus* is Latin for ball) that secrete mineralocorticoid hormones (primarily aldosterone).
2. The zona fasciculata is the middle zone and contains foamy-appearing cells in columns (*fascis* is Latin for bundle or stack) that secrete glucocorticoid hormones (primarily cortisol).
3. The zona reticularis is the inner zone of the cortex and contains cells in anastomosing cords (*rete* is Latin for net) that secrete androgens.
4. The adrenal medulla is sharply demarcated from the cortex and is composed of chromaffin cells with a deeply basophilic cytoplasm.

Chromaffin cells are modified neuroendocrine cells derived from the neural crest. They are **stimulated by acetylcholine** released by sympathetic preganglionic neurons and **secrete catecholamines** (80% epinephrine, 20% norepinephrine) directly into the bloodstream to amplify sympathetic nervous system activity.

(Choice B) ACTH stimulates secretion of glucocorticoid hormones from the zona fasciculata. Cortisol

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activity.

(Choice B) ACTH stimulates secretion of glucocorticoid hormones from the zona fasciculata. Cortisol produced in response to ACTH increases activity of the adrenal medullary enzyme phenylethanolamine N-methyltransferase, which catalyzes the conversion of norepinephrine to epinephrine. ACTH therefore indirectly upregulates medullary epinephrine production, but does not directly control it.

(Choice C) Aldosterone secretion from the zona glomerulosa is primarily regulated by angiotensin II and extracellular potassium levels.

(Choice D) Epinephrine released by the adrenal medulla acts on adrenergic receptors in the heart, lungs, liver, and skeletal muscle to increase sympathetic tone and mediate the acute stress response.

(Choice E) Most sympathetic *postganglionic* neurons release norepinephrine to activate adrenergic receptors on the target tissues. However, the *preganglionic* fibers innervating the adrenal medulla (and the postganglionic neurons innervating eccrine sweat glands) release acetylcholine.

Educational objective:
Chromaffin cells are modified neuroendocrine cells derived from the neural crest. Chromaffin cells in the adrenal medulla are stimulated by acetylcholine released by sympathetic preganglionic neurons and secrete catecholamines directly into the bloodstream to amplify sympathetic nervous system activity.

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Educational objective:
Chromaffin cells are modified neuroendocrine cells derived from the neural crest. Chromaffin cells in the adrenal medulla are stimulated by acetylcholine released by sympathetic preganglionic neurons and secrete catecholamines directly into the bloodstream to amplify sympathetic nervous system activity.

Histology Endocrine, Diabetes & Metabolism Pheochromocytoma

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A 56-year-old man with type 2 diabetes mellitus, hypertension, and hyperlipidemia comes to the office due to elevated blood glucose levels. The patient's current medications include metformin, lisinopril, and simvastatin. Blood pressure is 150/90 mm Hg and pulse is 88/min. BMI is 37 kg/m^2. Physical examination is unremarkable. Laboratory studies show a fasting glucose level of 156 mg/dL, serum creatinine of 1.1 mg/dL, hemoglobin A1c of 8.1%, and urine albumin-creatinine ratio of 200 mg/g (normal: <30). Treatment with empagliflozin is initiated. Which of the following effects is most likely to be seen with this new treatment?

A. Decrease in gastrointestinal absorption of glucose
B. Increase in body weight
C. Increase in endogenous insulin production
D. Reduction in glomerular hyperfiltration
E. Suppression of glucagon secretion

Submit

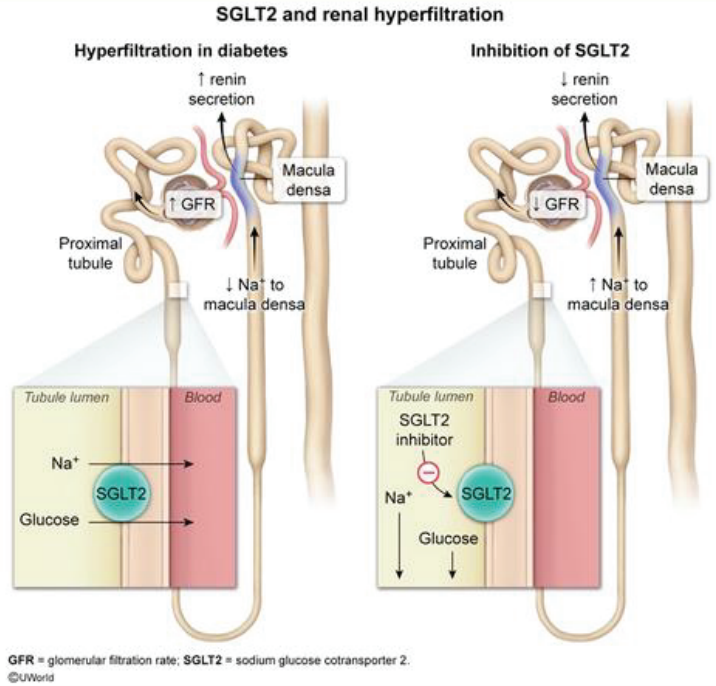
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A. Decrease in gastrointestinal absorption of glucose (19%)
B. Increase in body weight (7%)
C. Increase in endogenous insulin production (5%)
✓ D. Reduction in glomerular hyperfiltration (61%)
E. Suppression of glucagon secretion (5%)

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GFR = glomerular filtration rate; SGLT2 = sodium glucose cotransporter 2.
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This patient has incipient **diabetic nephropathy** with moderately increased albuminuria (ie, 30-300 mg/g). Although patients with more advanced diabetic kidney disease typically have reduced glomerular filtration (rising serum creatinine), in earlier stages, filtration is normal to increased and serum creatinine may be normal.

In the kidneys, filtered glucose is normally reabsorbed with sodium by **sodium-glucose cotransporter 2 (SGLT2)** in the proximal tubule. In patients with diabetes, the excess filtered glucose load causes increased reabsorption of sodium by SGLT2. This results in decreased sodium delivery to the macula densa, stimulating renin secretion by the juxtaglomerular apparatus and, ultimately, increasing angiotensin II levels. Angiotensin II induces relative vasoconstriction in the renal efferent arterioles, increasing hydrostatic pressure in the glomerular capillaries and causing **hyperfiltration**.

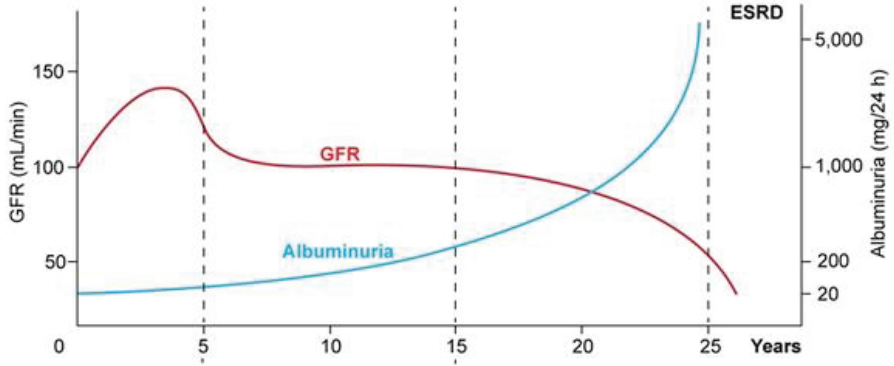
SGLT2 inhibitors (eg, empagliflozin) decrease the reabsorption of glucose and sodium in the proximal tubule, causing urine glucose wasting and lowering blood glucose. They also increase sodium delivery to the macula densa, which leads to decreased renin secretion, lower glomerular pressures, **reduced hyperfiltration**, and delayed progression of nephropathy.

(Choice A) Glucose is absorbed in the intestine primarily via SGLT1 (not SGLT2), which is not significantly affected by empagliflozin.

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Natural history of diabetic nephropathy



Hyperfiltration
- Glomerular hypertrophy
- ↑ GFR

Incipient DN
- Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis
- Moderately increased albuminuria
- Hypertension

Overt DN
- Mesangial nodules (Kimmelstiel-Wilson lesion), tubulointerstitial fibrosis
- Overt proteinuria
- Nephrotic syndrome
- ↓ GFR

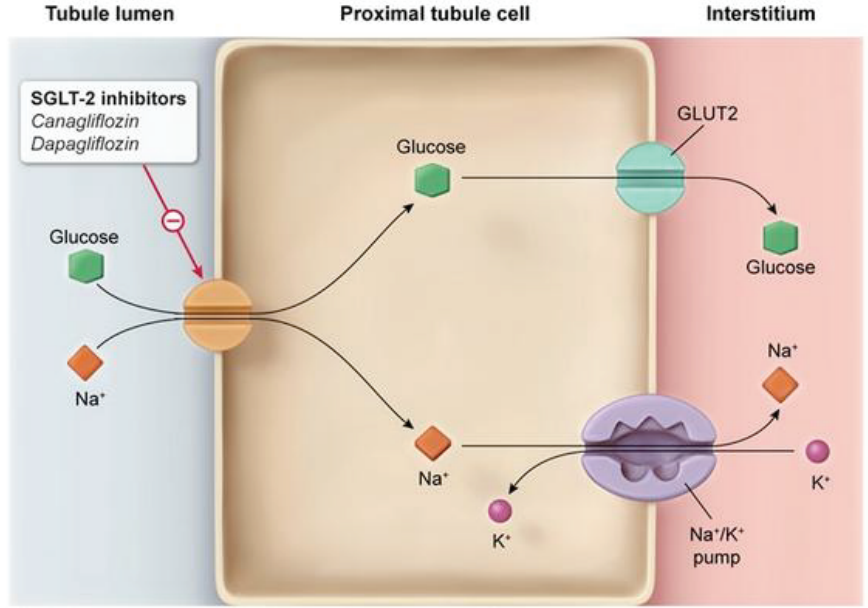
DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
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SGLT-2 inhibitors



GLUT2 = glucose transporter 2; SGLT-2 = sodium-glucose cotransporter 2.

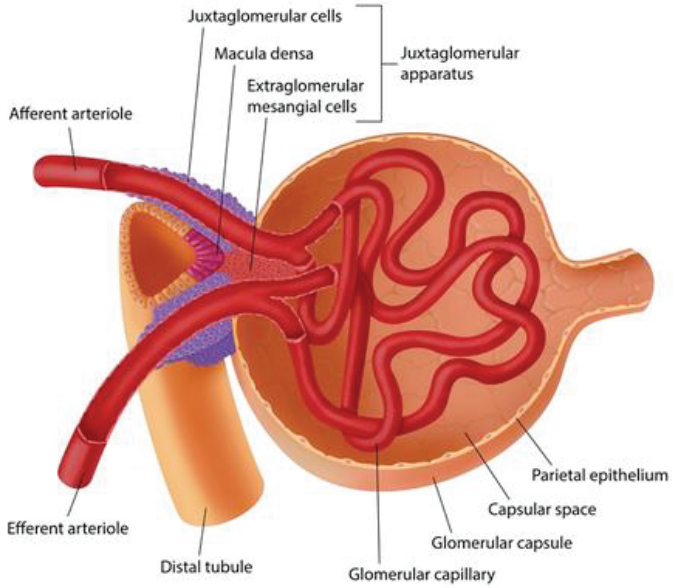
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Juxtaglomerular apparatus

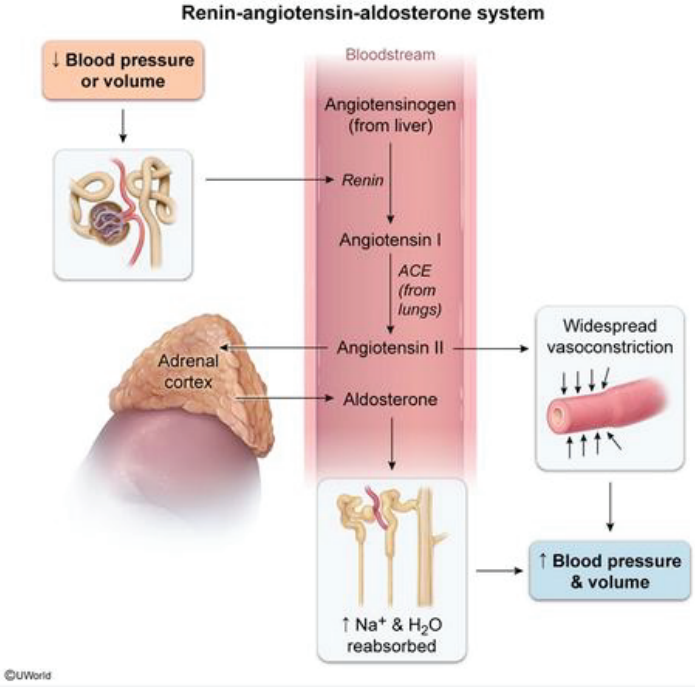


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tubule, causing urine glucose wasting and lowering blood glucose. They also increase sodium delivery to the macula densa, which leads to decreased renin secretion, lower glomerular pressures, **reduced hyperfiltration**, and delayed progression of nephropathy.

(Choice A) Glucose is absorbed in the intestine primarily via SGLT1 (not SGLT2), which is not significantly affected by empagliflozin.

(Choices B and C) Most patients on SGLT2 inhibitors experience modest weight loss, not gain, due to urinary glucose wasting and lower circulating insulin levels. SGLT2 inhibitors lower blood glucose, leading to decreased secretion of insulin by pancreatic beta cells.

(Choice E) SGLT2 inhibitors are associated with increased, not suppressed, glucagon secretion, possibly due to lower glucose and insulin levels or a direct effect on pancreatic alpha cells.

Educational objective:
In patients with diabetes, excess glucose in the proximal tubule causes increased reabsorption of sodium by sodium-glucose cotransporter 2 (SGLT2). This leads to decreased delivery of sodium to the macula densa and increased secretion of renin, ultimately increasing glomerular filtration pressure and causing hyperfiltration. SGLT2 inhibitors increase the delivery of sodium to the macula densa, decreasing renin production and reducing hyperfiltration.

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A 54-year-old woman is evaluated for a painless thyroid nodule. She has had no weight changes, heat or cold intolerance, hoarseness, or dyspnea. Medical history is notable for mild hypertension, for which she takes appropriate medications. The patient does not use tobacco or alcohol. Physical examination shows a 3-cm, firm nodule in the right thyroid lobe and enlarged, right cervical lymph nodes. TSH is normal, and fine-needle aspiration of the nodule shows papillary structures with nuclear atypia. Total thyroidectomy is planned. During the surgery, a nearby nerve is injured while ligating an artery entering the superior pole of the thyroid lobe. Which of the following muscles is most likely to be denervated as a result of this injury?

A. Aryepiglotticus
B. Cricothyroid
C. Lateral cricoarytenoid
D. Posterior cricoarytenoid
E. Thyroarytenoid

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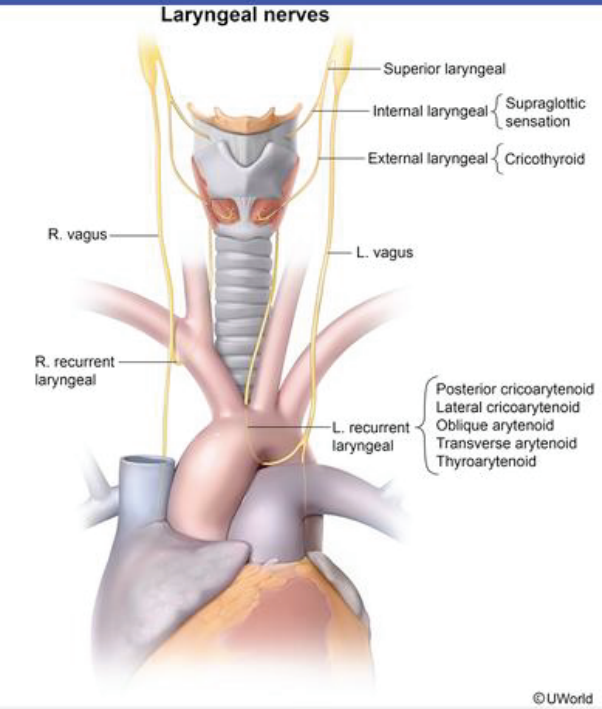
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- A. Aryepiglotticus (3%)
- ✓ B. Cricothyroid (69%)
- C. Lateral cricoarytenoid (12%)
- D. Posterior cricoarytenoid (7%)
- E. Thyroarytenoid (6%)

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The superior thyroid artery (a branch of the external carotid artery) and the inferior thyroid artery (a branch of the thyrocervical trunk) provide the blood supply to the thyroid and parathyroid glands. The **superior thyroid artery** and vein and **external branch of the superior laryngeal nerve** course together in a neurovascular triad that originates superior to the thyroid gland and lateral to the thyroid cartilage. The external branch is at risk of injury during thyroidectomy as it courses just deep to the superior thyroid artery.

The **cricothyroid muscle** is the only muscle innervated by this nerve. It originates on the cricoid cartilage and inserts on the lower border of the thyroid cartilage. The cricothyroid muscle acts to tense the vocal cords, and denervation injury may cause a low, hoarse voice with limited range of pitch. The internal branch of the superior laryngeal nerve does not innervate any muscles but provides sensory innervation to the laryngeal mucosa above the vocal folds.

(Choices A, C, D, and E) The remaining laryngeal muscles are innervated by the recurrent laryngeal nerves, which also provide sensory innervation to the larynx below the vocal folds. The recurrent laryngeal nerves lie posterior to the thyroid, near the inferior thyroid arteries. These nerves can be injured during thyroidectomy but do not run with the superior thyroid artery at the superior pole of the thyroid.

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(Choices A, C, D, and E) The remaining laryngeal muscles are innervated by the recurrent laryngeal nerves, which also provide sensory innervation to the larynx below the vocal folds. The recurrent laryngeal nerves lie posterior to the thyroid, near the inferior thyroid arteries. These nerves can be injured during thyroidectomy but do not run with the superior thyroid artery at the superior pole of the thyroid.

Educational objective:

The external branch of the superior laryngeal nerve is at risk of injury during thyroidectomy due to its proximity to the superior thyroid artery and vein. This nerve innervates the cricothyroid muscle.

References

- Identification of the external branch of the superior laryngeal nerve during thyroidectomy.

Anatomy	Endocrine, Diabetes & Metabolism	Thyroid cancer
Subject	System	Topic

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A 22-year-old primigravida who recently emigrated from the Dominican Republic has a normal vaginal delivery. The infant is phenotypically male but has hypospadias and a small phallus. The testes are well developed but reside in the inguinal area. His physical examination, including blood pressure, is otherwise normal. Serum testosterone level is within normal limits. A karyotype is performed and shows 46,XY. Which of the following enzymes is most likely deficient in this patient?

- A. 5α-reductase
- B. 17-hydroxylase
- C. 21-hydroxylase
- D. Aromatase
- E. DHEA sulfatase

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A 22-year-old primigravida who recently emigrated from the Dominican Republic has a normal vaginal delivery. The infant is phenotypically male but has hypospadias and a small phallus. The testes are well developed but reside in the inguinal area. His physical examination, including blood pressure, is otherwise normal. Serum testosterone level is within normal limits. A karyotype is performed and shows 46,XY. Which of the following enzymes is most likely deficient in this patient?

- ✓ A. 5α-reductase (71%)
- B. 17-hydroxylase (8%)
- C. 21-hydroxylase (6%)
- D. Aromatase (6%)
- E. DHEA sulfatase (6%)

Correct

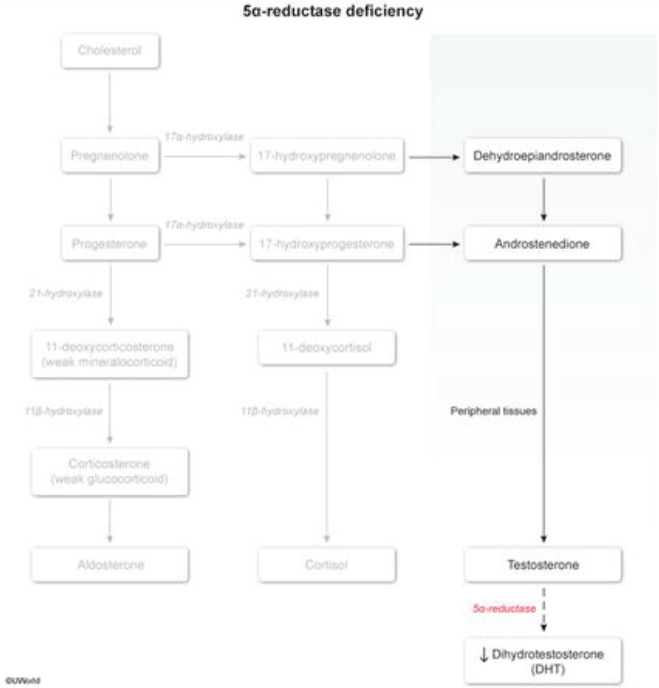
71% Answered correctly

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Sexual development is influenced predominantly by 3 hormones:

- **Testosterone**: Development of internal male genitalia, spermatogenesis, male sexual differentiation at puberty (muscle mass, libido)
- **Dihydrotestosterone** (DHT): Development of external male genitalia, growth of prostate, male-pattern hair growth; also amplifies effects of testosterone due to high affinity for testosterone receptor.
- **Estrogen**: Endometrial proliferation, development of ovarian granulosa cells, breast development

5α-reductase converts testosterone to DHT. There are 2 types of 5α-reductase; type 1 is present in postpubescent skin, whereas type 2 is found predominantly in the genitals. Deficiency of **5α-reductase type 2** results in diminished conversion of testosterone to DHT in the male urogenital tract. In the male fetus with this genetic defect, the internal genitalia develop normally under the influence of testosterone, but the external genitalia do not develop properly due to the lack of DHT, resulting in **male pseudohermaphroditism**. The genitalia at birth can range from a small phallus with hypospadias to ambiguous or female-type genitalia. Such children are often raised as females until they reach puberty, when high levels of testosterone and the action of 5α-reductase type 1 result in masculinization with male-pattern muscle mass, voice deepening, penile and scrotal growth, and testicular descent.

(Choice B) Deficiency of 17-hydroxylase results in decreased secretion of cortisol and sex steroids and an

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increased level of mineralocorticoids. This deficiency manifests clinically with sodium retention, leading to hypertension and undervirilization of male infants (female-type genitalia).

(Choice C) 21-hydroxylase converts 17-hydroxyprogesterone to 11-deoxycortisol, and progesterone to 11-deoxycorticosterone. Deficiency of 21-hydroxylase causes corticosteroid precursors to be shunted toward androgen production, resulting in virilization of the female fetus and salt wasting. Male children have salt wasting and normal genitalia.

(Choice D) Aromatase catalyzes the conversion of androgens to estrogens in the gonads and peripheral tissues. Aromatase deficiency presents with virilization of female infants; male patients are not affected phenotypically.

(Choice E) Dehydroepiandrosterone (DHEA) sulfate is a weak androgen produced by the adrenal cortex. Deficiency of DHEA sulfatase does not result in undervirilization of the male fetus.

Educational objective:
5α-reductase converts testosterone to dihydrotestosterone, which mediates development of the external genitalia in the male fetus. Male neonates with 5α-reductase deficiency are born with feminized external genitalia that typically masculinize at puberty. A small phallus and hypospadias are common.

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A 58-year-old man comes to the office for evaluation of a foot wound. The patient noticed a small ulcer on the bottom of his right foot a week ago but recalls no significant foot injury. He has been applying antiseptics, but the wound has failed to heal. The patient has a 15-year history of type 2 diabetes mellitus and is nonadherent to medical therapy. He has smoked a pack of cigarettes daily for 20 years. Temperature is 37.1 C (98.8 F), blood pressure is 140/80 mm Hg, and pulse is 72/min. Right lower extremity examination shows a 1-cm (0.39-in) plantar ulcer under the first metatarsal head. There are no other lesions, and the tibial and dorsalis pedis pulses are normal. Which of the following is the major inciting factor responsible for this patient's foot ulcer?

A. Atherosclerotic disease
B. Bacterial infection
C. Irritant dermatitis
D. Sensory impairment
E. Systemic vasculitis
F. Venous insufficiency

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antiseptics, but the wound has failed to heal. The patient has a 15-year history of type 2 diabetes mellitus and is nonadherent to medical therapy. He has smoked a pack of cigarettes daily for 20 years. Temperature is 37.1 C (98.8 F), blood pressure is 140/80 mm Hg, and pulse is 72/min. Right lower extremity examination shows a 1-cm (0.39-in) plantar ulcer under the first metatarsal head. There are no other lesions, and the tibial and dorsalis pedis pulses are normal. Which of the following is the major inciting factor responsible for this patient's foot ulcer?

A. Atherosclerotic disease (10%)
B. Bacterial infection (1%)
C. Irritant dermatitis (0%)
✓ D. Sensory impairment (73%)
E. Systemic vasculitis (5%)
F. Venous insufficiency (7%)

Correct
73%
27 secs
10/01/2020

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Lower extremity ulcers			
	Arterial insufficiency	**Venous insufficiency**	**Neuropathic**
Common location	Tips of toes, malleoli	Medial tibia	Bony prominences, plantar surfaces
Clinical features	Sharply demarcated, pale base; deep	Irregular, shallow, erythematous base with granulation tissue & exudate	Sharply demarcated, erythematous base
Pain	Very painful	Moderate pain	None
Skin changes	Hairless, shiny, cold	Brown/hyperpigmentation, erythema, thickened skin	Dry, scaly, calloused
Pulses	Decreased/absent	Present	Present
Associated	Smoking, hypertension,	Deep vein thrombosis, varicose veins, pregnancy,	Diabetes mellitus, other

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Clinical features	Sharply demarcated, pale base; deep	Irregular, shallow, erythematous base with granulation tissue & exudate	Sharply demarcated, erythematous base
Pain	Very painful	Moderate pain	None
Skin changes	Hairless, shiny, cold	Brown/hyperpigmentation, erythema, thickened skin	Dry, scaly, calloused
Pulses	Decreased/absent	Present	Present
Associated conditions	Smoking, hypertension, atherosclerosis	Deep vein thrombosis, varicose veins, pregnancy, increased age	Diabetes mellitus, other peripheral neuropathy
Treatment	Revascularization, antiplatelet agents	Compression, elevation	Pressure offloading

This patient has a plantar ulcer under the first metatarsal head. In a patient with chronic, poorly controlled **diabetes mellitus**, this is likely a **neuropathic ulcer** due to underlying peripheral **sensory neuropathy**.

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This patient has a plantar ulcer under the first metatarsal head. In a patient with chronic, poorly controlled **diabetes mellitus**, this is likely a **neuropathic ulcer** due to underlying peripheral **sensory neuropathy**. Chronic hyperglycemia promotes nerve injury and impairs nerve repair in distal sensory fibers, causing decreased sensation of pain, pressure, and proprioception.

Loss of these protective senses can cause individuals to not recognize an injury due to minor trauma, friction, or **pressure**. Areas that are particularly susceptible are points of localized pressure created by a shoe or weight-bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in this area often goes unnoticed (due to lack of pain sensation and being hidden by socks or shoes) and can develop into a nonhealing foot ulcer.

Loss of proprioception and an increase in ligamentous laxity can also cause chronic pressure-induced joint/skin damage in the feet of patients with diabetic neuropathy, which can lead to calluses or foot deformities (eg, Charcot foot, hammer toe).

(Choice A) Although diabetic patients (especially those who smoke) often have comorbid arterial insufficiency, arterial ulcers are typically painful, sharply demarcated, and located at the tips of the toes. This patient has full distal pulses, which makes clinically significant atherosclerotic disease unlikely to be the primary cause of the ulcer.

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the primary cause of the ulcer.

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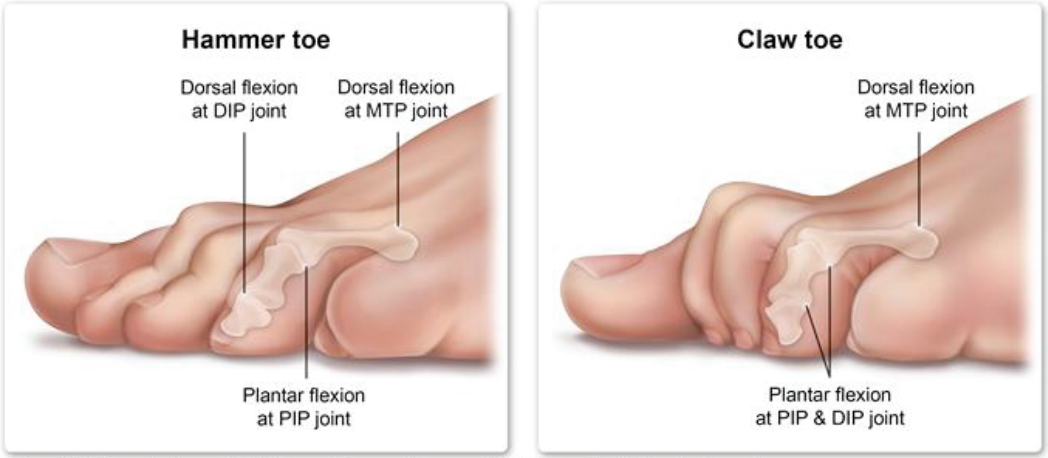
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the primary cause of the ulcer.

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Hammer & claw toe deformities



DIP = distal interphalangeal; **MTP** = metatarsophalangeal; **PIP** = proximal interphalangeal.
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the primary cause of the ulcer.

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deformities (eg, Charcot foot, hammer toe).

(Choice A) Although diabetic patients (especially those who smoke) often have comorbid arterial insufficiency, arterial ulcers are typically painful, sharply demarcated, and located at the tips of the toes. This patient has full distal pulses, which makes clinically significant atherosclerotic disease unlikely to be the primary cause of the ulcer.

(Choice B) Bacterial infection may delay ulcer healing, especially if there is underlying osteomyelitis, but it is not the inciting cause of neuropathic ulcers. In addition, although diabetic ulcers are often colonized by bacteria, this patient has no fever, erythema, or purulent drainage to suggest serious infection.

(Choice C) Irritant contact dermatitis presents with pruritic or painful erythema in areas of exposed skin (eg, hands). It can occasionally cause small vesicles or fissures, but ulcers are not typical.

(Choice E) Systemic vasculitic disorders (eg, polyarteritis nodosa) are an uncommon cause of skin ulcers. Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms.

(Choice F) Ulcers caused by venous insufficiency are most common over the tibias or proximal to the medial malleolus. They present as irregular ulcerations in the setting of stasis dermatitis and/or varicose veins.

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(Choice E) Systemic vasculitic disorders (eg, polyarteritis nodosa) are an uncommon cause of skin ulcers. Vasculitic ulcers are usually painful and associated with other skin (eg, purpura, nodules) and systemic (eg, fever, fatigue) symptoms.

(Choice F) Ulcers caused by venous insufficiency are most common over the tibias or proximal to the medial malleolus. They present as irregular ulcerations in the setting of stasis dermatitis and/or varicose veins.

Educational objective:

Neuropathic foot ulcers can occur in diabetic patients when loss of pain sensation and proprioception delays recognition of injury due to trauma, friction, or sustained pressure (on plantar surface of foot bones). The risk is greatest in patients with longstanding diabetes who have poor glycemic control.

References

- The diabetic foot.

Pathology	Endocrine, Diabetes & Metabolism	Diabetic foot
Subject	System	Topic

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shoe or weight-bearing bones of the foot (eg, plantar surface of the **first metatarsal head**). A wound in

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A 50-year-old man comes to the physician for a routine check-up. He has a 20-pack-year smoking history and consumes alcohol occasionally. He eats a balanced diet and consumes fried foods and red meat several times a week. He is not very active and spends much of his free time watching television and sitting at his computer. His family history is significant for hypertension in his mother and bladder cancer in his father. His blood pressure is 160/90 mm Hg and heart rate is 70/min. Laboratory testing is significant for a fasting blood glucose level of 155 mg/dL. Which of the following interventions is likely to have the greatest effect on reducing this patient's mortality risk?

A. Annual fecal occult blood test
B. Annual prostate-specific antigen test
C. Daily aspirin
D. Dietary modification
E. Regular exercise
F. Smoking cessation
G. Tight glycemic control

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several times a week. He is not very active and spends much of his free time watching television and sitting at his computer. His family history is significant for hypertension in his mother and bladder cancer in his father. His blood pressure is 160/90 mm Hg and heart rate is 70/min. Laboratory testing is significant for a fasting blood glucose level of 155 mg/dL. Which of the following interventions is likely to have the greatest effect on reducing this patient's mortality risk?

- A. ~~Annual fecal occult blood test~~ (0%)
- B. ~~Annual prostate-specific antigen test~~ (0%)
- C. Daily aspirin (3%)
- D. Dietary modification (7%)
- E. Regular exercise (11%)
- ✓ F. Smoking cessation (67%)
- G. Tight glycemic control (8%)

Correct

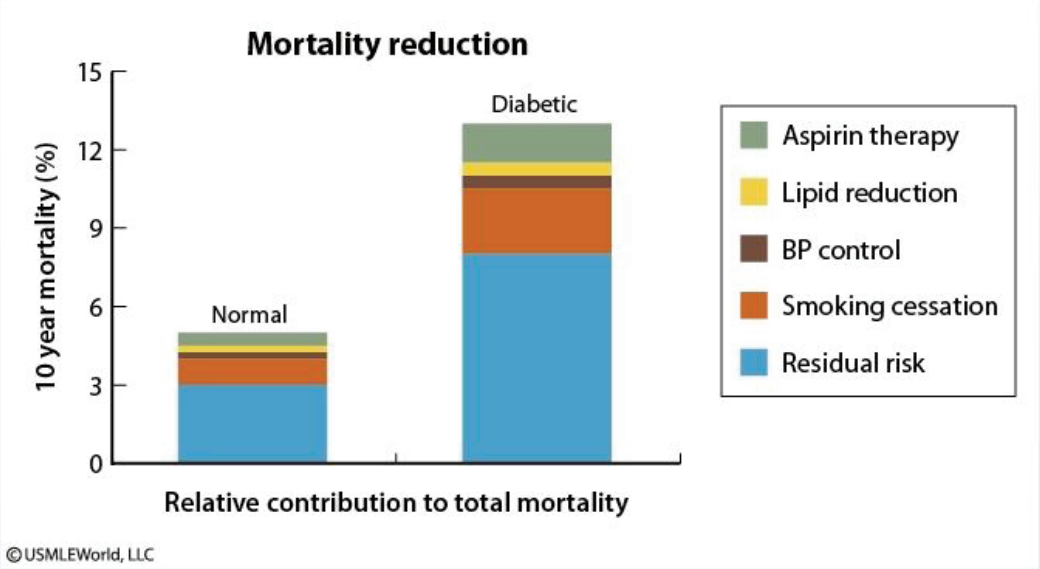
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Explanation



One of the objectives for the national Healthy People 2020 initiative is to reduce the prevalence of tobacco smoking in adults from 20% in 2008 to less than 12% by 2020. Tobacco use, especially smoking, is the single most preventable cause of death and disease in the United States. In addition to its numerous direct

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One of the objectives for the national Healthy People 2020 initiative is to reduce the prevalence of tobacco smoking in adults from 20% in 2008 to less than 12% by 2020. Tobacco use, especially smoking, is the single most preventable cause of death and disease in the United States. In addition to its numerous direct adverse effects, tobacco smoking also substantially increases the risk for macrovascular (eg, myocardial infarction [MI], stroke) and microvascular (eg, retinopathy, nephropathy) complications of diabetes mellitus. These complications significantly increase mortality, primarily by increasing the risk of MI. The risk of MI-associated mortality begins to decrease immediately upon smoking cessation. However, it takes several tobacco-free years before the risk returns to baseline, especially in patients with a long history of smoking. In addition, smokers with diabetes have a higher likelihood of developing hypercholesterolemia, poor glycemic control, and end-stage renal disease. It appears that smoking not only worsens the complications of diabetes but also increases the likelihood of developing diabetes in the first place, thus highlighting the importance of prevention and early cessation.

(Choice A) Fecal occult blood testing screens for colorectal cancer and improves mortality through earlier detection. Even so, the mortality benefit is much lower than that achieved by smoking cessation.

(Choice B) Prostate-specific antigen is increased in some patients with prostate cancer. However, annual prostate-specific antigen testing has not been shown to improve mortality from prostate cancer.

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(Choice A) Fecal occult blood testing screens for colorectal cancer and improves mortality through earlier detection. Even so, the mortality benefit is much lower than that achieved by smoking cessation.

(Choice B) Prostate-specific antigen is increased in some patients with prostate cancer. However, annual prostate-specific antigen testing has not been shown to improve mortality from prostate cancer.

(Choice C) Aspirin use significantly reduces the risk of death from coronary heart disease in diabetic patients, at levels similar to smoking cessation. However, when all-cause mortality is compared, smoking cessation has a greater effect on reducing mortality than daily aspirin therapy.

(Choices D, E, and G) Dietary modification and exercise reduce the risk of cardiovascular disease (to a lesser extent than smoking cessation) and help improve glycemic control in diabetic individuals. Although tight glycemic control has been shown to reduce the risk of microvascular complications from diabetes, it does not significantly improve cardiovascular or all-cause mortality.

Educational objective:
Smoking cessation is by far the most effective preventive intervention in almost all patients, and this is especially true in those with diabetes.

References

- How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic

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A 4-day-old infant is brought to the emergency department with abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as poor feeding, vomiting, and irritability for the past 2 days. The mother also reports that his diapers smell like "caramelizing sugar." There are no known medical problems in the family, but the child's maternal aunt died "sometime in the first year" of life from unknown causes. Examination shows a lethargic infant with intermittent posturing episodes and increased generalized muscle tone. Laboratory studies of plasma and urine confirm the diagnosis. In addition to appropriate dietary restriction, supplementation with which of the following may improve this infant's condition?

- A. Arginine
- B. Cobalamin
- C. Pyridoxine
- D. Tetrahydrobiopterin
- E. Thiamine

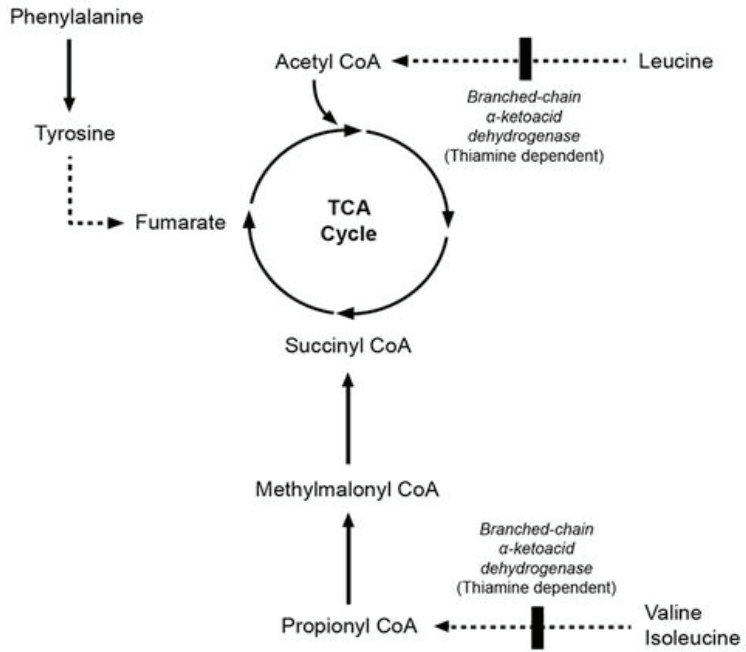
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- A. Arginine (15%)
- B. Cobalamin (5%)
- C. Pyridoxine (18%)
- D. Tetrahydrobiopterin (19%)
- ✓ E. Thiamine (41%)

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This infant has symptoms typical of **maple syrup urine disease (MSUD)**, an autosomal recessive disorder characterized by the defective breakdown of branched-chain amino acids (**leucine**, **isoleucine**, and **valine**). Degradation of these 3 amino acids first involves transamination to their respective α-ketoacids, which are subsequently metabolized by several enzymes referred to as the **branched-chain α-ketoacid dehydrogenase complex** (BCKDC).

Mutations in BCKDC result in accumulation of the branched-chain amino acids in serum and peripheral tissues, resulting in **neurotoxicity** that includes seizures, irritability, lethargy, and poor feeding. A metabolite of isoleucine gives the urine a distinctive **sweet odor**. MSUD can be life-threatening if untreated, as brain swelling may lead to death.

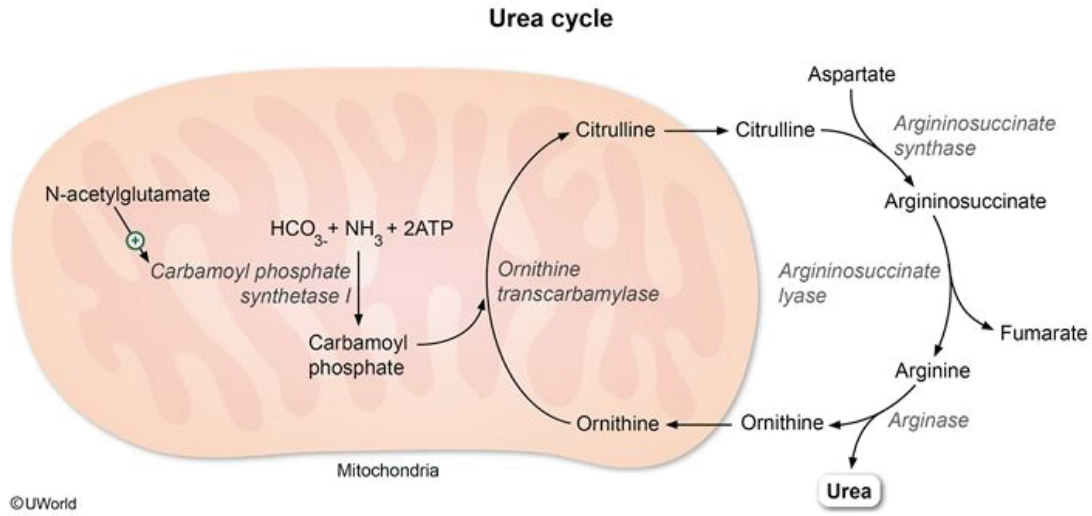
Branched-chain α-ketoacid dehydrogenase (in addition to pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) requires 5 cofactors: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with MSUD improve with high-dose **thiamine treatment**, but most still require lifelong dietary restrictions.

(Choice A) Most disorders of the urea cycle require arginine as an essential amino acid. When patients with urea cycle disorders develop hyperammonemia, arginine is administered for production of downstream

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still require lifelong dietary restrictions.

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Educational objective:

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hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism, as well as heme and neurotransmitter synthesis. Pyridoxine supplementation is also used in the treatment of hyperhomocysteinemia.

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria, as tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:

Branched-chain α-ketoacid dehydrogenase requires several coenzymes: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with maple syrup urine disease improve with high-dose thiamine treatment, but most require lifelong restriction of leucine, isoleucine, and valine.

References

- Branched-chain amino acid metabolism: From rare Mendelian diseases to more common disorders.
- Maple syrup urine disease.

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A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise. His symptoms improve after drinking orange juice or eating a protein bar. The patient was diagnosed with type 2 diabetes 6 months ago and advised to lose weight with dietary modification and exercise. Since then, he has been working out intensively and has lost 10 kg (22 lb). Which of the following mechanisms is responsible for this patient's symptoms when exercising?

A. Decreased hepatic glucose production
B. Increased glucokinase activity
C. Increased glucose-6-phosphatase activity
D. Translocation of glucose transporter 2 to the cell membrane
E. Translocation of glucose transporter 4 to the cell membrane

Submit

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A 46-year-old man develops episodes of "dizzy spells" accompanied by palpitations and sweating during exercise. His symptoms improve after drinking orange juice or eating a protein bar. The patient was diagnosed with type 2 diabetes 6 months ago and advised to lose weight with dietary modification and exercise. Since then, he has been working out intensively and has lost 10 kg (22 lb). Which of the following mechanisms is responsible for this patient's symptoms when exercising?

A. Decreased hepatic glucose production (18%)
B. Increased glucokinase activity (8%)
C. Increased glucose-6-phosphatase activity (6%)
D. Translocation of glucose transporter 2 to the cell membrane (7%)
✓ E. Translocation of glucose transporter 4 to the cell membrane (58%)

Correct

58%
Answered correctly

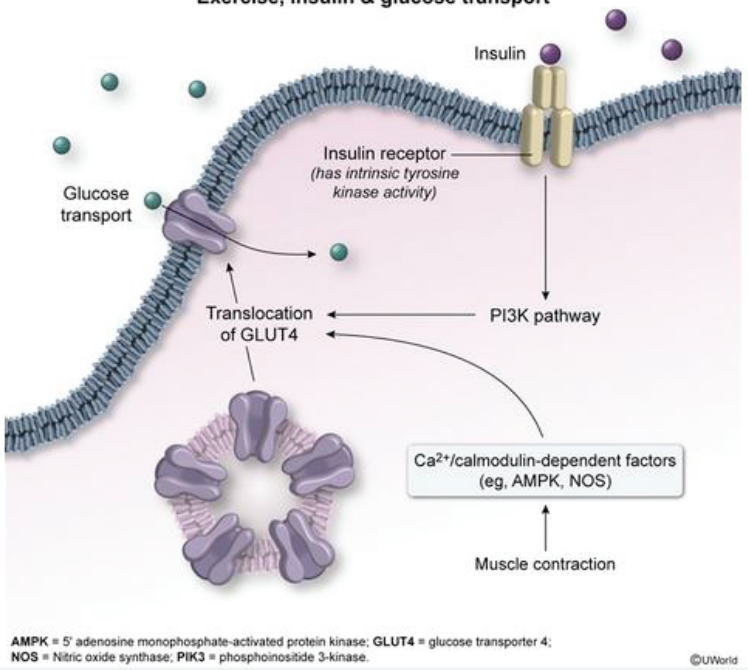
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Exercise, insulin & glucose transport



AMPK = 5' adenosine monophosphate-activated protein kinase; **GLUT4** = glucose transporter 4; **NOS** = Nitric oxide synthase; **PIK3** = phosphoinositide 3-kinase.

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AMPK = 5' adenosine monophosphate-activated protein kinase; **GLUT4** = glucose transporter 4; **NOS** = Nitric oxide synthase; **PIK3** = phosphoinositide 3-kinase.

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Glucose uptake in skeletal muscle occurs by facilitated diffusion via glucose transporter (GLUT) 4. In the fed state, **insulin** induces muscular glucose uptake by stimulating **translocation of GLUT4** from intracellular depots to the plasma membrane and T tubules. As circulating glucose and insulin levels fall in the fasting state, GLUT4 is resequestered, and muscle becomes increasingly dependent on internal stores of glucose and glycogen and, subsequently, on fatty acids released by lipolysis in the liver.

However, translocation of GLUT4 is also induced by **muscle contraction**, allowing insulin-independent **glucose uptake during exercise**. Over time, regular exercise also causes increased expression of GLUT4 and greater insulin-dependent GLUT4 translocation, leading to increased skeletal muscle glucose uptake at any given insulin level (ie, increased insulin sensitivity) and therefore lower blood glucose.

This patient has been engaging in a regular exercise program and is likely experiencing rapid uptake of glucose while exercising. As blood glucose levels fall, counterregulatory factors (eg, glucagon, epinephrine) are activated, leading to his symptoms (eg, palpitations, sweating), which are then relieved by the intake of sugar. **Exercise-induced hypoglycemia** is common in patients with diabetes mellitus due to the lack of physiologic insulin regulation along with insufficient carbohydrate supplementation.

(Choice A) As blood glucose levels fall during fasting or exercise, glucagon and epinephrine stimulate

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(Choice A) As blood glucose levels fall during fasting or exercise, glucagon and epinephrine stimulate hepatic glycogenolysis and gluconeogenesis, leading to increased (not decreased) glucose production.

(Choice B) Glucokinase phosphorylates glucose to glucose-6-phosphate, primarily for glycogen synthesis. It is expressed mainly in the liver and is stimulated by rising, not falling, glucose levels.

(Choice C) Glucose-6-phosphatase catalyzes the hydrolysis of glucose-6-phosphate to glucose during gluconeogenesis, thereby helping to maintain glucose levels in the fasting state; increased activity would improve hypoglycemic symptoms by increasing circulating glucose levels.

(Choice D) GLUT2 is found primarily in the liver and pancreatic beta cells, where it facilitates insulin-independent glucose uptake. It is not expressed significantly in muscle or translocated in response to muscle contraction.

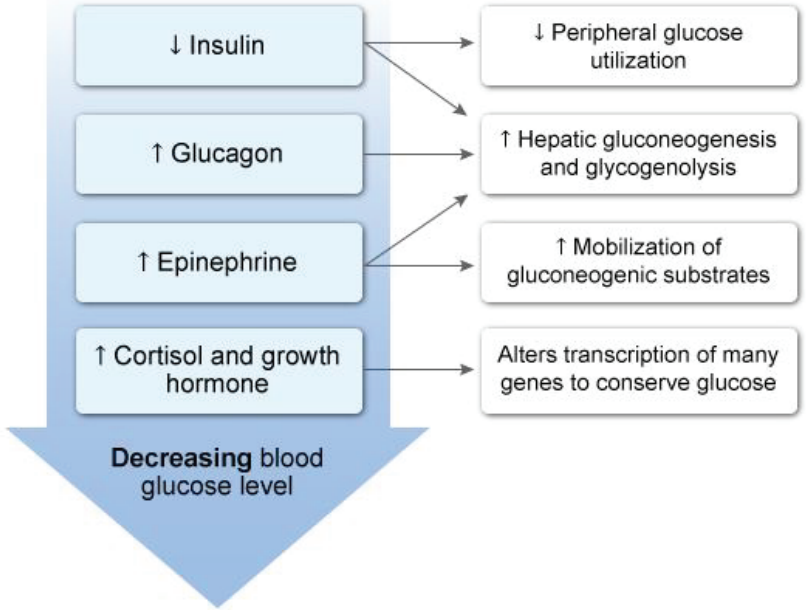
Educational objective:

Glucose uptake in skeletal muscle occurs primarily via glucose transporter (GLUT) 4. Muscle contraction and insulin induce translocation of GLUT4 to the cell surface, increasing glucose uptake during exercise and the fed state, respectively. Over time, regular exercise causes increased expression of GLUT4, leading to increased skeletal muscle glucose uptake at any given insulin level and therefore lower blood glucose levels.

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Physiologic defense against hypoglycemia



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A 13-year-old girl is brought to the clinic by her mother for a yearly physical examination. The patient feels well but is worried that she has not yet started puberty. Temperature is 36.7 C (98 F), blood pressure is 152/91 mm Hg, pulse is 75/min, and respirations are 18/min. Physical examination is significant for a lack of secondary sexual characteristics; a blind vagina is noted on pelvic examination. Laboratory studies reveal hypokalemia and low testosterone and estradiol levels. Cytogenetic analysis shows a 46,XY karyotype. This patient most likely has deficiency of which of the following enzymes?

- A. 5 alpha-reductase
- B. 11 beta-hydroxylase
- C. 17 alpha-hydroxylase
- D. 20,22-desmolase
- E. 21-hydroxylase

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- A. 5 alpha-reductase (11%)
- B. 11 beta-hydroxylase (11%)
- ✓ C. 17 alpha-hydroxylase (66%)
- D. 20,22-desmolase (2%)
- E. 21-hydroxylase (8%)

Correct

66% Answered correctly

51 secs Time Spent

09/11/2020 Last Updated

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Congenital adrenal hyperplasia				
Enzyme deficiency	**Mineralocorticoids**	**Glucocorticoids**	**Androgens**	**Symptoms**
21-hydroxylase	↓	↓	↑	• Salt wasting (vomiting, hypotension, ↓ Na^+, ↑ K^+) • Ambiguous genitalia in girls
11β-hydroxylase	↑*	↓	↑	• Hypertension, ↓ K^+ • Ambiguous genitalia in girls
17α-hydroxylase	↑	↑**	↓	• Hypertension, ↓ K^+ • Ambiguous genitalia in boys • Absent puberty
*Low aldosterone but excessive weak mineralocorticoid (11-deoxycorticosterone).				

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This patient is genetically male (46,XY) with features suggestive of 17 alpha-hydroxylase deficiency, a rare cause of **congenital adrenal hyperplasia** (CAH). The enzyme 17 alpha-hydroxylase is active in the adrenal glands and gonads and is responsible for converting pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. Deficiency of this enzyme **impairs synthesis of sex hormones** (eg, testosterone, estradiol) and cortisol but **does not inhibit mineralocorticoid production**.

Due to the absence of androgens in utero, genetic males (46,XY) with 17 alpha-hydroxylase deficiency have undervirilized, ambiguous genitalia. In severe cases, they appear **phenotypically female** but lack internal female genitalia, as in this case. In contrast, genetic females (46,XX) develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones in the gonads leads to **absent secondary sexual characteristics** in both sexes and primary amenorrhea in girls.

Excess mineralocorticoid production results in **hypertension** and **hypokalemia** that are usually detected around the expected time of **puberty**. Low cortisol provides positive feedback to increase ACTH production, further stimulating the mineralocorticoid pathway. This allows for the excess production of weak glucocorticoids (ie, corticosterone), preventing the detrimental effects of low cortisol.

(Choice A) 5 alpha-reductase deficiency prevents conversion of testosterone to dihydrotestosterone, the hormone responsible for male external genitalia development. Affected genetic males have ambiguous

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(Choice A) 5 alpha-reductase deficiency prevents conversion of testosterone to dihydrotestosterone, the hormone responsible for male external genitalia development. Affected genetic males have ambiguous genitalia at birth but develop normal secondary sexual characteristics (eg, increased muscle mass, phallus enlargement) at puberty because these features are testosterone dependent. Blood pressure and electrolytes are unaffected.

(Choice B) 11 beta-hydroxylase deficiency causes decreased glucocorticoid synthesis and increased production of adrenal androgens. Because the production of 11-deoxycorticosterone (weak mineralocorticoid) is also increased, individuals with this deficiency have features of mineralocorticoid excess (eg, hypertension, hypokalemia). However, genetic males appear phenotypically normal.

(Choice D) 20,22-desmolase (side chain cleavage enzyme) deficiency results in impaired synthesis of all steroid hormones with accumulation of cholesterol esters in the adrenal glands and gonads. Complete deficiency is lethal, and partial deficiency typically presents in infancy with signs of adrenal insufficiency (eg, hypotension, hyperkalemia).

(Choice E) The most common form of CAH is 21-hydroxylase deficiency. It causes decreased glucocorticoid and mineralocorticoid synthesis and increased adrenal androgen production. In contrast to this patient, genetic males with 21-hydroxylase deficiency appear phenotypically normal

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mineralocorticoid) is also increased, individuals with this deficiency have features of mineralocorticoid excess (eg, hypertension, hypokalemia). However, genetic males appear phenotypically normal.

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(Choice E) The most common form of CAH is 21-hydroxylase deficiency. It causes decreased glucocorticoid and mineralocorticoid synthesis and increased adrenal androgen production. In contrast to this patient, genetic males with 21-hydroxylase deficiency appear phenotypically normal.

Educational objective:

Deficiency of 17 alpha-hydroxylase is a rare form of congenital adrenal hyperplasia characterized by impaired synthesis of androgens, estrogens, and cortisol with excess production of mineralocorticoids. Genetic males with this deficiency may have phenotypically female external genitalia and present with hypertension and hypokalemia around the expected time of puberty.

References

- Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic.

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A 20-year-old woman comes to the emergency department with lethargy, abdominal pain, and nausea. She has had polyuria and excessive thirst for one day. She also complains of dysuria and chills over the last few days but did not seek medical care until today. Physical examination shows tachycardia and dry mucous membranes. Laboratory results are as follows:

Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

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Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores
A.	Decreased	Decreased
B.	Decreased	Increased
C.	Increased	Decreased
D.	Increased	Increased
E.	No Change	No change

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Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores	
A.	~~Decreased~~	~~Decreased~~	(6%)
B.	~~Decreased~~	~~Increased~~	(12%)
✓ C.	Increased	Decreased	(77%)
D.	Increased	Increased	(2%)
E.	~~No Change~~	~~No change~~	(0%)

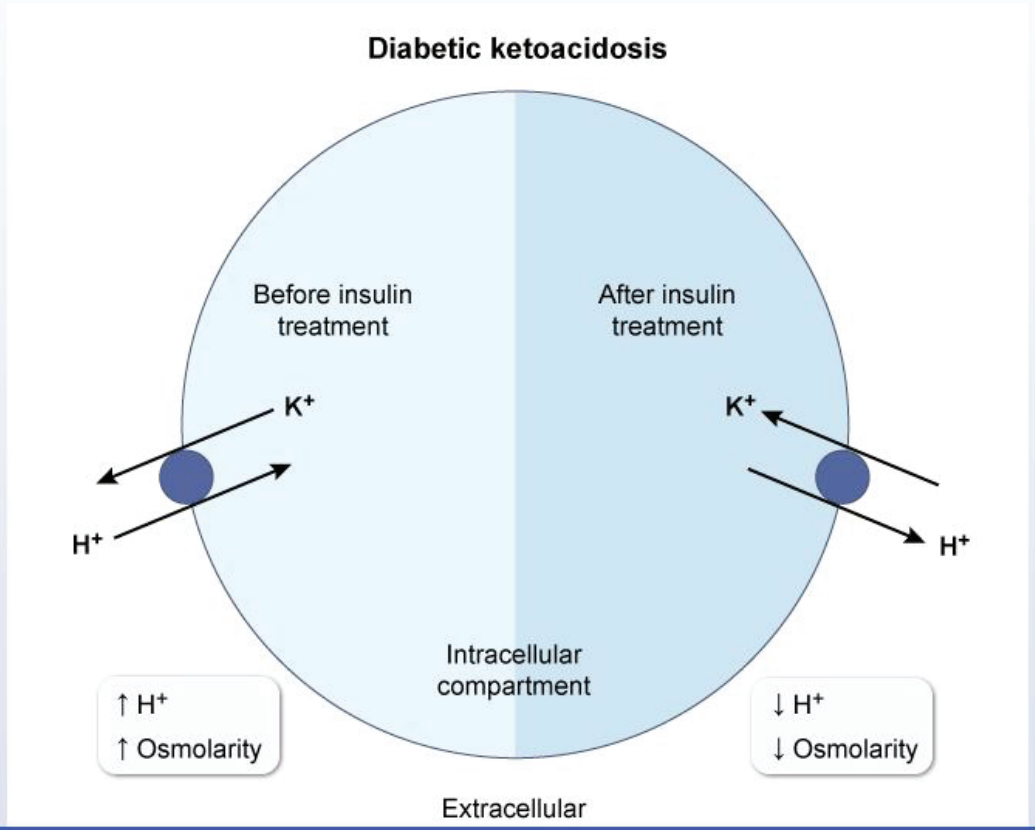
Correct

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This young patient has both clinical (eg, polyuria, polydipsia, volume depletion) and biochemical (eg, hyperglycemia, low bicarbonate, high anion gap, decreased serum sodium levels) signs of diabetic ketoacidosis (DKA). DKA is often precipitated by infections, including urinary tract infections (likely in this patient). Patients with DKA lose significant amounts of potassium in the urine, primarily via glycosuria-induced osmotic diuresis and hypovolemia-mediated increase in aldosterone secretion. This results in a **total body potassium deficit** that is reflected by decreased intracellular potassium stores (since 98% of the body's potassium is stored intracellularly). Despite the low intracellular potassium levels, **extracellular potassium concentrations are normal or increased** due to the following mechanisms:

1. Loss of intracellular free water caused by increased plasma osmolality leads to extracellular movement of potassium secondary to increasing intracellular potassium concentration
2. Lack of insulin also causes extracellular shifting of potassium as insulin normally promotes cellular uptake of potassium

Clinicians must be careful when giving insulin and intravenous fluids during resuscitation of dehydrated, hyperglycemic patients. These interventions force potassium back into the cells, causing a precipitous drop in serum potassium due to the total body deficit. Despite normal or elevated serum potassium, timely administration of potassium supplementation is essential when treating a patient with DKA.

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administration of potassium supplementation is essential when treating a patient with DKA.

(Choice A) A decrease in both intra- and extracellular potassium levels is seen with mineralocorticoids excess, diuretic use, and chronic gastrointestinal losses.

(Choice B) Extracellular potassium concentration decreases following glucose and insulin administration as potassium moves into the intracellular compartment. Stimulation of beta-adrenergic receptors also causes increased transfer of potassium to the intracellular compartment.

(Choice D) Renal excretion of potassium is impaired in most patients with chronic renal failure, resulting in increased total body potassium storage and hyperkalemia.

(Choice E) Normal extracellular potassium levels are common in patients with DKA as the extracellular potassium shift is often mitigated by increased urinary potassium losses. However, intracellular potassium levels are always decreased in DKA.

Educational objective:
Most patients with diabetic ketoacidosis have normal to increased serum potassium levels despite a total body potassium deficit. Replacement of potassium is a crucial step in the management of patients with diabetic ketoacidosis.

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A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral enlargement and partial fusion of the labioscrotal folds. The patient has also had high blood pressure recorded on 3 consecutive office visits. She has been tracking at the 50th percentile for height and weight, and has not had any other medical problems. Family history is noncontributory. Laboratory studies are significant for moderate hypokalemia. Cytogenetic studies show a 46,XX karyotype. Which of the following enzymes is most likely deficient in this patient?

A. 5α-reductase
B. 11β-hydroxylase
C. 17α-hydroxylase
D. 21-hydroxylase
E. Side-chain cleavage enzyme

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- A. 5α-reductase (1%)
- ✓ B. 11β-hydroxylase (56%)
- C. 17α-hydroxylase (21%)
- D. 21-hydroxylase (20%)
- E. Side-chain cleavage enzyme (0%)

Correct

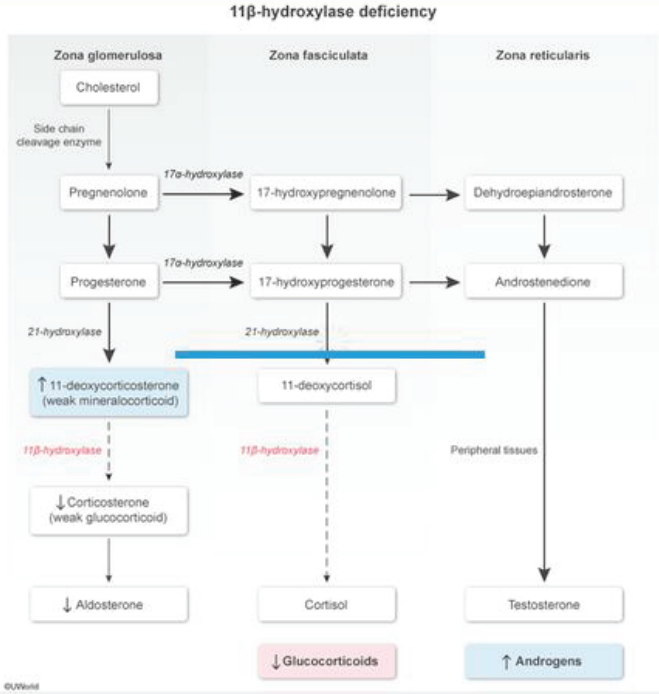
56% Answered correctly

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This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11β-hydroxylase deficiency**, the second-most common cause of congenital adrenal hyperplasia after 21-hydroxylase deficiency.

11β-hydroxylase is responsible for converting 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. Enzyme deficiency results in the buildup of aldosterone and cortisol precursors, which are then shunted toward adrenal androgen synthesis. In genetically female infants, **androgen excess** leads to **ambiguous genitalia** (virilization). Although 11β-hydroxylase deficiency inhibits aldosterone synthesis, **11-deoxycorticosterone** accumulates and acts as a weak mineralocorticoid, causing affected individuals to have **hypertension** and **hypokalemia**.

(Choice A) 5α-reductase deficiency causes ambiguous genitalia in boys due to the defective conversion of testosterone to dihydrotestosterone. Girls have normal genitalia, and blood pressure and electrolytes are unaffected.

(Choice C) 17α-hydroxylase deficiency results in impaired sex steroid and cortisol synthesis, and increased production of mineralocorticoids. Girls are born with normal genitalia, but boys are born undervirilized (ambiguous genitalia). Affected individuals develop hypertension and hypokalemia (mineralocorticoid excess) and do not undergo puberty (no sex steroids).

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Congenital adrenal hyperplasia

Enzyme deficiency	Mineralocorticoids	Glucocorticoids	Androgens	Symptoms
21-hydroxylase	↓	↓	↑	• Salt wasting (vomiting, hypotension, ↓ Na^+, ↑ K^+) • Ambiguous genitalia in girls
11β-hydroxylase	↑*	↓	↑	• Hypertension, ↓ K^+ • Ambiguous genitalia in girls
17α-hydroxylase	↑	↑**	↓	• Hypertension, ↓ K^+ • Ambiguous genitalia in boys • Absent puberty

*Low aldosterone but excessive weak mineralocorticoid (11-deoxycorticosterone).
**Low cortisol but excessive weak glucocorticoid (corticosterone).

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unaffected.

(Choice C) 17α-hydroxylase deficiency results in impaired sex steroid and cortisol synthesis, and increased production of mineralocorticoids. Girls are born with normal genitalia, but boys are born undervirilized (ambiguous genitalia). Affected individuals develop hypertension and hypokalemia (mineralocorticoid excess) and do not undergo puberty (no sex steroids).

(Choice D) 21-hydroxylase deficiency decreases glucocorticoid and mineralocorticoid synthesis and increases adrenal androgen production. Girls are born with ambiguous genitalia (androgen excess) and frequently develop hypotension and hyperkalemia (mineralocorticoid deficiency).

(Choice E) Side-chain cleavage enzyme converts cholesterol to pregnenolone. Because this is the first enzyme in the steroidogenic pathway, deficiency impairs synthesis of all steroid hormones. Complete deficiency is lethal due to absent placental progesterone synthesis.

Educational objective:
11β-hydroxylase deficiency typically results in excessive adrenal androgen and mineralocorticoid (11-deoxycorticosterone) production. Genetically female infants are born with ambiguous genitalia, and affected individuals develop hypertension and hypokalemia early in life.

References

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A 34-year-old man develops excessive thirst and frequent urination while being hospitalized for multiple injuries following a motorcycle collision. His urinary osmolality after 4 hours of water restriction is 250 mOsm/L and increases to 700 mOsm/L after administration of antidiuretic hormone. The patient is started on an appropriate medication, and his symptoms promptly resolve. Over the next 2 years, multiple attempts are made to wean the patient off the medication, but his symptoms would always return, necessitating the resumption of treatment. The permanence of this patient's condition is best explained by traumatic damage to which of the following structures?

A. Anterior pituitary
B. Hypothalamic nuclei
C. Kidneys
D. Posterior pituitary
E. Thalamic nuclei

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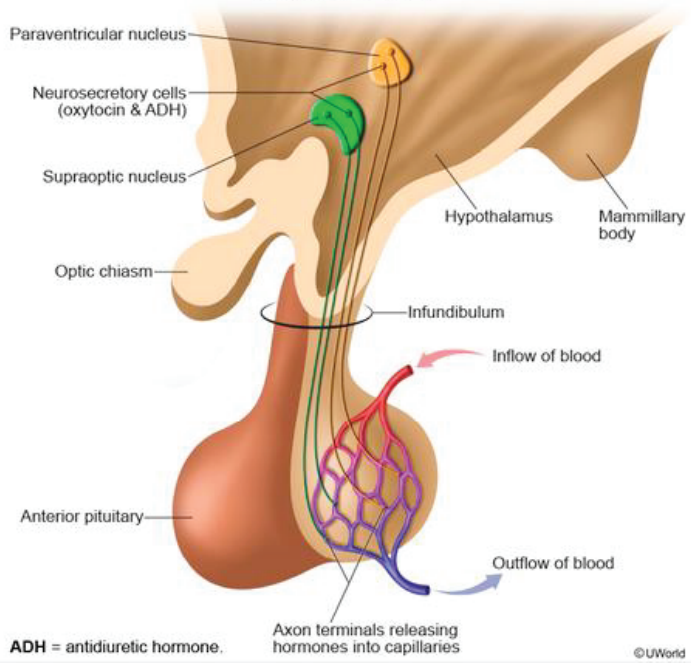
A. Anterior pituitary (5%)
B. Hypothalamic nuclei (46%)
C. Kidneys (2%)
D. Posterior pituitary (45%)
E. Thalamic nuclei (0%)

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Exhibit Display

Neurohypophysis



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This patient has **diabetes insipidus** (DI), a condition that results in the production of large volumes of very dilute urine due to impaired antidiuretic hormone (ADH) activity. DI can be due to deficient ADH production in the brain **(central)** or resistance to ADH in the kidneys (nephrogenic). Injection of exogenous ADH can help distinguish between central and nephrogenic DI: **ADH administration** substantially **increases urine osmolality** in patients with central DI, whereas patients with nephrogenic DI typically have a more limited increase in urine osmolality (<300 mOsm/L increase).

ADH is synthesized by magnocellular neurosecretory cells in the paraventricular and supraoptic nuclei of the hypothalamus. These neurons project axons to the posterior pituitary where axon terminals store large quantities of ADH for later release into the circulation. Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central DI. Damage to the more distal portions of the hypothalamic-hypophyseal tract (ie, below the infundibulum) typically causes transient DI because the cell bodies of the magnocellular neurons remain intact. However, **hypothalamic injury** results in death of the magnocellular neurons, causing **permanent central DI**.

(Choice A) The anterior pituitary produces ACTH, TSH, gonadotrophic hormones, prolactin, and growth hormone. Hormone secretion from the anterior pituitary is regulated by substances released from the median eminence into the hypothalamic-hypophyseal portal vessels.

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median eminence into the hypothalamic-hypophyseal portal vessels.

(Choice C) Although head trauma is a frequent cause of central DI, traumatic damage to the kidneys does not result in nephrogenic DI. Furthermore, this patient's large increase in urine concentration following ADH administration is more suggestive of central DI.

(Choice D) Isolated posterior pituitary damage most often causes transient central DI because the cell bodies of the magnocellular neurons remain intact and can undergo axonal regeneration to allow adequate ADH release into the circulation.

(Choice E) Thalamic nuclei are involved in relaying sensory and motor signals to the cerebral cortex and in regulating alertness and consciousness.

Educational objective:
Injury to the hypothalamus or posterior pituitary (eg, head trauma, transsphenoidal neurosurgery, suprasellar masses) can result in central diabetes insipidus (DI). Damage to the posterior pituitary gland typically causes transient DI, whereas damage to the hypothalamic nuclei often causes permanent DI.

References

- Diabetes Insipidus after Traumatic Brain Injury

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A 33-year-old man comes to the office due to episodic headaches for several months accompanied by sweating and feelings of anxiety that spontaneously resolve after 15-30 minutes. He has no other medical conditions and takes no medications. His brother recently had surgery to treat hyperparathyroidism. Blood pressure is 180/110 mm Hg, and pulse is 102/min. Laboratory results show normal serum electrolytes and renal function. CT scan of the abdomen reveals a mass in the right adrenal gland. Which of the following cells have the same embryological origin as the tissue responsible for this patient's current condition?

A. Capillary endothelial cells
B. Cardiac myocytes
C. Interstitial fibroblasts
D. Melanin-producing cells
E. Thyroid follicular cells

Submit

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A 33-year-old man comes to the office due to episodic headaches for several months accompanied by sweating and feelings of anxiety that spontaneously resolve after 15-30 minutes. He has no other medical conditions and takes no medications. His brother recently had surgery to treat hyperparathyroidism. Blood pressure is 180/110 mm Hg, and pulse is 102/min. Laboratory results show normal serum electrolytes and renal function. CT scan of the abdomen reveals a mass in the right adrenal gland. Which of the following cells have the same embryological origin as the tissue responsible for this patient's current condition?

A. ~~Capillary endothelial cells~~ (1%)
B. ~~Cardiac myocytes~~ (2%)
C. ~~Interstitial fibroblasts~~ (0%)
✓ D. Melanin-producing cells (80%)
E. Thyroid follicular cells (14%)

Correct

80%
Answered correctly

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Embryological derivatives		
Ectoderm	Surface ectoderm	• Anterior pituitary (Rathke pouch) • Lens & cornea • Inner ear sensory organs, olfactory epithelium • Nasal & oral epithelial linings, salivary glands • Epidermis, sweat & mammary glands
	Neural tube	• Brain & spinal cord • Posterior pituitary, pineal gland • Retina
	Neural crest	• Neural ganglia, adrenal medulla • Schwann cells; pia & arachnoid mater • Aorticopulmonary septum & endocardial cushions • Branchial arches (bones & cartilage) • Skull bones • Melanocytes

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	• Melanocytes
Mesoderm	• Muscles (skeletal, cardiac & smooth) • Connective tissue, bone & cartilage • Serosal linings (eg, peritoneum) • Cardiovascular & lymphatic system • Spleen & hemopoietic cells • Kidney & ureters, internal genitalia • Adrenal cortex
Endoderm	• Gastrointestinal tract, liver, pancreas • Lungs • Thymus, parathyroids, thyroid follicular cells • Middle ear epithelium • Bladder & urethra • Parafollicular (C) cells*

*Formerly thought to be of neural crest origin.

This patient with severe hypertension, headaches, and an adrenal mass has typical features of

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This patient with severe hypertension, headaches, and an adrenal mass has typical features of **pheochromocytoma**, a catecholamine-secreting tumor of the chromaffin cells of the adrenal medulla. Pheochromocytoma can be sporadic or associated with several familial disorders, especially **multiple endocrine neoplasia (MEN) type 2** (particularly likely in this patient given his family history of hyperparathyroidism). MEN type 2 is associated with germ-line mutations in the *RET* proto-oncogene and is characterized by:

- Pheochromocytomas
- Medullary thyroid cancer (malignancy of parafollicular C cells)
- Either parathyroid hyperplasia (MEN 2A) or mucosal neuromas and marfanoid habitus (MEN 2B)

Neural crests are embryological structures composed of parallel strips of cells arising from the ectoderm at the margin of the neural tube. The chromaffin cells of the **adrenal medulla** are derived from neural crest tissue (the adrenal cortex is derived from the mesoderm). Structures arising from neural crest cells can be remembered with the mnemonic "SOME SALT" (Schwann cells, odontoblasts, **melanocytes**, enterochromaffin cells, spinal membranes [pia and arachnoid], **adrenal medulla**/ganglia, laryngeal cartilage, tracheal cartilage).

(Choices A, B, and C) Capillary endothelial cells and cardiac myocytes are mesodermal derivatives that

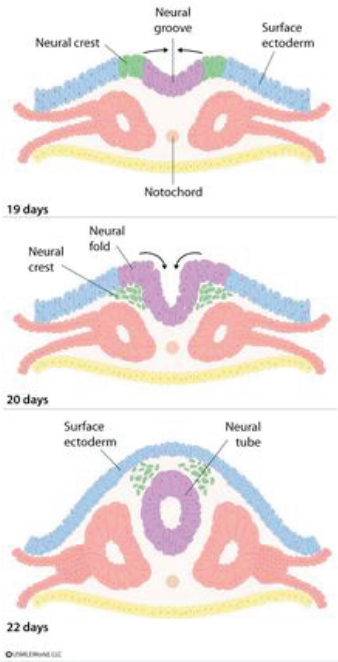
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This patient with severe hypertension, headaches, and an adrenal mass has typical features of

Exhibit Display

Neural tube formation



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cartilage, tracheal cartilage).

(Choices A, B, and C) Capillary endothelial cells and cardiac myocytes are mesodermal derivatives that arise from primitive endothelium. Interstitial fibroblasts also arise from the mesoderm.

(Choice E) Thyroid follicular cells are an endodermal derivative, arising from the pharyngeal epithelium at the base of the tongue. Although the parafollicular, calcitonin-secreting C cells were previously thought to originate from neural crest tissue, recent studies suggest that they have an endodermal origin.

Educational objective:

Neural crests are embryological structures composed of parallel strips of cells arising from the ectoderm at the margin of the neural tube. Structures derived from neural crest cells include Schwann cells, odontoblasts, melanocytes, enterochromaffin cells, spinal membranes, adrenal medulla/ganglia, laryngeal cartilage, and tracheal cartilage.

References

- Familial pheochromocytomas and paragangliomas.
- The neural crest: a versatile organ system.

Embryology Endocrine, Diabetes & Metabolism Pheochromocytoma

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A 17-year-old boy who was recently diagnosed with type 1 diabetes mellitus is found unresponsive at home. His family reports that the patient did not feel good last night and skipped dinner, but he still took his usual dose of insulin. Paramedics find that his fingerstick blood glucose is 32 mg/dL and immediately administer intramuscular glucagon. Glucagon binds to a transmembrane receptor in hepatocytes, which promotes binding of intracellular GTP to a specific receptor-associated protein. This leads to further downstream signaling and rapid metabolic changes within hepatocytes, including a rapid decrease in intracellular glycogen stores and release of glucose into the blood. Which of the following is the most likely mediator responsible for these effects?

A. cGMP-dependent protein kinase
B. Janus tyrosine kinase
C. Phosphodiesterase
D. Protein kinase A
E. Tyrosine-specific protein kinase

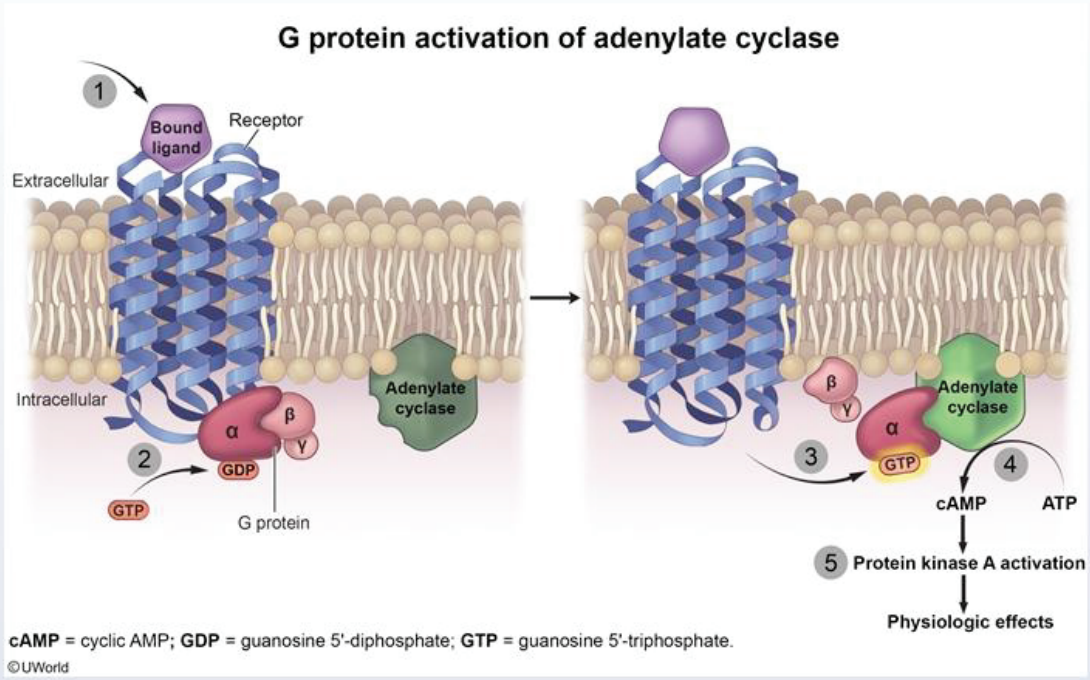
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home. His family reports that the patient did not feel good last night and skipped dinner, but he still took his usual dose of insulin. Paramedics find that his fingerstick blood glucose is 32 mg/dL and immediately administer intramuscular glucagon. Glucagon binds to a transmembrane receptor in hepatocytes, which promotes binding of intracellular GTP to a specific receptor-associated protein. This leads to further downstream signaling and rapid metabolic changes within hepatocytes, including a rapid decrease in intracellular glycogen stores and release of glucose into the blood. Which of the following is the most likely mediator responsible for these effects?

A. cGMP-dependent protein kinase (18%)
B. ~~Janus tyrosine kinase~~ (6%)
C. ~~Phosphodiesterase~~ (3%)
✓ D. Protein kinase A (61%)
E. ~~Tyrosine-specific protein kinase~~ (10%)

Correct
61%
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Glucagon exerts its effects through G protein-coupled receptors using the **adenylate cyclase second messenger system**. G protein is a heterotrimer consisting of alpha, beta, and gamma subunits associated with the intracellular domain of these transmembrane receptors. The alpha subunit of the inactivated G

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Glucagon exerts its effects through G protein-coupled receptors using the **adenylate cyclase second messenger system**. G protein is a heterotrimer consisting of alpha, beta, and gamma subunits associated with the intracellular domain of these transmembrane receptors. The alpha subunit of the inactivated G protein is bound to GDP. On **receptor activation**, the alpha subunit undergoes a conformational change, which releases GDP and binds GTP. **GTP binding** allows the alpha subunit to dissociate from the remainder of the G protein complex.

There are multiple subtypes of alpha G proteins, each with different secondary effects. A specific alpha subunit known as **G_s** (present in glucagon, TSH, and PTH receptor complexes) **activates adenylate cyclase** when released from the G protein complex. Adenylate cyclase converts ATP to **cAMP**, which activates **protein kinase A**. Protein kinase A phosphorylates specific serine/threonine residues in various enzymes, leading to their activation or deactivation. Protein kinase A also phosphorylates proteins that bind to the regulatory regions of genes on DNA.

(Choice A) cGMP activates protein kinase G, which mediates a number of intracellular effects (eg, smooth muscle relaxation, platelet activation, sperm metabolism). cGMP is inactivated by cGMP phosphodiesterase, which cleaves cGMP in the corpus cavernosum of the penis and regulates penile erection. Drugs that inhibit cGMP-specific phosphodiesterase (eg, sildenafil) are used in the treatment of erectile dysfunction.

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erectile dysfunction.

(Choice B) Janus tyrosine kinase (JAK) is a cytoplasmic protein activated by ligand binding to non-G protein-coupled transmembrane receptors that lack intrinsic tyrosine kinase activity. Growth hormone, erythropoietin, and cytokines (eg, interferon) are common ligands for these receptors. JAKs activate cytoplasmic transcription factors called STATs (signal transducers and activators of transcription), which enter the nucleus to promote gene transcription.

(Choice C) cAMP is cleaved by the enzyme cAMP phosphodiesterase to its inactive form, 5'-AMP. Drugs that inhibit cAMP phosphodiesterase lead to prolongation of the actions of cAMP. An example is the use of theophylline in bronchial asthma.

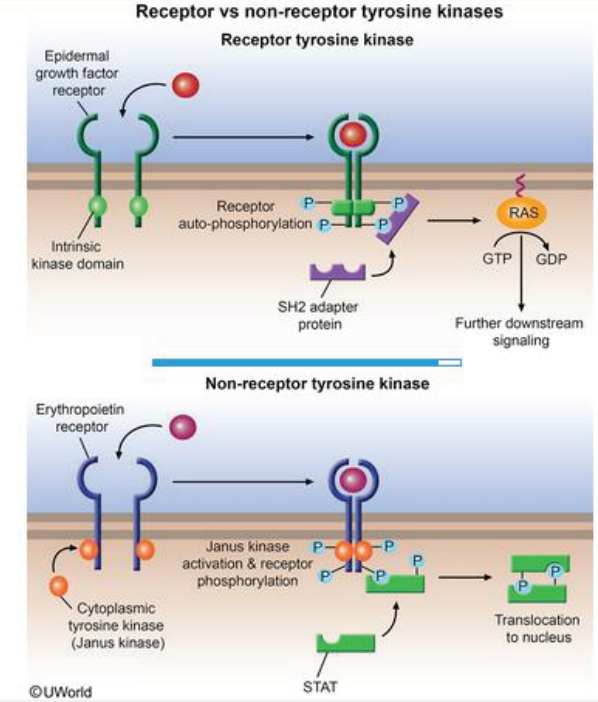
(Choice E) Ligands such as insulin and epidermal growth factor act through transmembrane receptors that have intrinsic tyrosine kinase domains.

Educational objective:
Protein kinase A is responsible for the intracellular effects of the G protein-mediated adenylate cyclase second messenger system. Hormone receptors that use this system include the TSH, glucagon, and PTH receptors.

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A 2-hour-old newborn has a blood glucose concentration of 30 mg/dL. The patient was delivered via caesarean to a 32-year-old woman at 38 weeks gestation. Birth weight is 4.5 kg (9 lb 14 oz). The pregnancy was complicated by gestational diabetes treated with insulin. However, glycemic control remained suboptimal due to maternal noncompliance with insulin treatment and poor adherence to dietary recommendations. Examination of the neonate is unremarkable. Which of the following is the most likely primary mechanism responsible for this patient's low blood glucose concentration?

A. Decreased glycogen stores
B. Hyperfunctioning pancreas
C. Impaired hepatic glycogenolysis
D. Increased release of cortisol
E. Insulin resistance

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- A. ~~Decreased glycogen stores~~ (4%)
- ✓ B. Hyperfunctioning pancreas (77%)
- C. ~~Impaired hepatic glycogenolysis~~ (7%)
- D. ~~Increased release of cortisol~~ (1%)
- E. Insulin resistance (8%)

Correct

77% Answered correctly

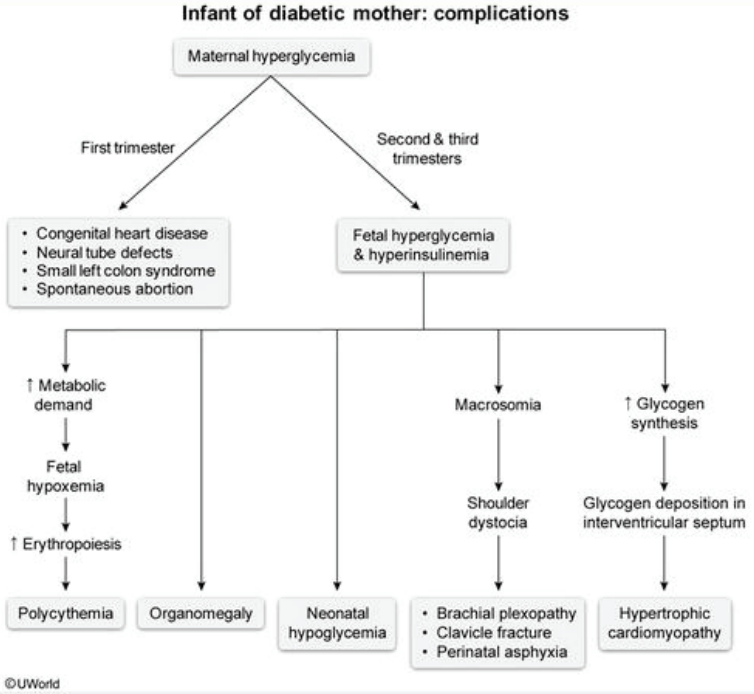
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Glucose levels fall in all newborns after birth, but usually remain ≥40 mg/dL due to mobilization of hepatic glycogen stores and initiation of feeding; glucose <40 mg/dL is indicative of **neonatal hypoglycemia**, a common metabolic derangement seen in **infants of diabetic mothers**.

During gestation, glucose is transferred continuously from mother to fetus via the placenta. Mothers with diabetes, particularly those with poor glycemic control, often have hyperglycemia, causing **fetal hyperglycemia**. In utero, this results in compensatory **hyperfunctioning of pancreatic beta cells**, which then produce increased amounts of insulin to handle the excessive glucose load. Once the maternal glucose supply is interrupted at delivery, persistent **hyperinsulinemia** causes increased glucose consumption and transient neonatal hypoglycemia.

Most neonates with hypoglycemia are asymptomatic but may develop autonomic symptoms (eg, jitteriness, irritability) and, if severe, hypotonia and seizures. **Macrosomia** (>4 kg [8 lb 14 oz] birth weight) is also common in infants of diabetic mothers due to increased exposure to growth factors (eg, insulin, insulin-like growth factors, growth hormone) that stimulate fetal growth and increased deposition of glycogen and fat in developing tissues **(Choice A)**.

(Choice C) Hypoglycemia due to impaired hepatic glycogenolysis is characteristic of certain glycogen storage diseases (eg, von Gierke disease, Cori disease), which typically present within the first several

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developing tissues **(Choice A)**.

(Choice C) Hypoglycemia due to impaired hepatic glycogenolysis is characteristic of certain glycogen storage diseases (eg, von Gierke disease, Cori disease), which typically present within the first several months of life with failure to thrive, ketotic hypoglycemia, and hepatomegaly (ie, protruding abdomen) due to increased hepatic glycogen content.

(Choices D and E) Critically ill infants may produce increased cortisol due to stress (eg, sepsis, mechanical ventilation) with resultant hyperglycemia. Insulin resistance, which is not typically seen in infants but is related to obesity in children and adults, also causes hyperglycemia. However, this neonate is hypoglycemic.

Educational objective:
Neonatal hypoglycemia is common in infants of diabetic mothers. The pathophysiology involves maternal hyperglycemia, which in turn causes fetal hyperglycemia and compensatory hyperfunctioning of the pancreas (ie, hyperinsulinemia). After birth, persistently elevated insulin levels lead to transient hypoglycemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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A 42-year-old woman comes to the physician for a routine check-up. She has no current complaints and no significant past medical history. On physical examination, the physician notes lesions on her eyelids that are pictured below.

Which of the following is the best next step in the management of this patient?

A. ECG and serum cardiac enzymes
B. Serum lipids and blood glucose level
C. Liver function tests and abdominal ultrasonography
D. Complete blood count and stool guaiac test
E. Slit lamp exam and ophthalmoscopy
F. Lesion biopsy and surgeon referral

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E. Slit lamp exam and ophthalmoscopy

F. Lesion biopsy and surgeon referral

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Which of the following is the best next step in the management of this patient?

- A. ECG and serum cardiac enzymes (0%)
- ✓ B. Serum lipids and blood glucose level (93%)
- C. ~~Liver function tests and abdominal ultrasonography~~ (3%)
- D. ~~Complete blood count and stool guaiac test~~ (0%)
- E. ~~Slit lamp exam and ophthalmoscopy~~ (0%)
- F. ~~Lesion biopsy and surgeon referral~~ (0%)

Correct

93%

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The lesion pictured is a xanthelasma, a type of xanthoma usually found on the medial eyelids. Hyperlipidemia and/or dyslipidemia can result in xanthomas (including xanthelasmas). Xanthelasmas are dermal accumulations of benign-appearing macrophages with abundant, finely vacuolated (foamy) cytoplasm containing cholesterol (free and esterified), phospholipids, and triglycerides. Due in part to insulin resistance promoting increased VLDL production, diabetics may develop a secondary Type IV or V hyperlipidemia (increased VLDL, chylomicrons) and/or a secondary diabetic dyslipidemia with elevated LDL cholesterol and low HDL cholesterol. Thus, in order to determine the type of this patient's lipid disorder and to rule out underlying diabetes, her serum lipids and blood glucose should be measured.

(Choice A) Although this patient may be at increased risk for coronary artery disease due to hyperlipidemia or dyslipidemia, she does not currently have symptoms of myocardial infarction. Her current management should be focused on treating her lipid disorder.

(Choice C) The first step in managing this patient is to establish what type of lipid abnormality she has based upon her serum lipid levels and lipoprotein profile. If the results are consistent with an obstructive liver and/or biliary system lesion producing cholestasis and hypercholesterolemia, then liver function tests and abdominal ultrasonography may be warranted.

(Choice D) A CBC and stool guaiac test are performed when searching for occult GI bleeding.

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liver and/or biliary system lesion producing cholestasis and hypercholesterolemia, then liver function tests and abdominal ultrasonography may be warranted.

(Choice D) A CBC and stool guaiac test are performed when searching for occult GI bleeding.

(Choice E) Slit lamp examination and funduscopy could reveal ocular findings associated with this patient's lipid disorder, such as a corneal arcus (lipid deposit) or lipemia retinalis. However, a serum lipid profile should be obtained next in order to establish the type of hyperlipidemia or dyslipidemia in this patient.

(Choice F) Xanthelasmas are usually diagnosed based on clinical appearance. Biopsy is not required. Treatment is primarily medical and directed at the underlying lipid abnormality. Surgical excision is not medically necessary, but may be undertaken electively for cosmetic reasons.

Educational objective:
Xanthelasmas, a type of xanthoma, are yellowish macules/papules found on the medial eyelids. They are dermal accumulations of macrophages containing cholesterol and triglycerides, and are generally associated with a primary or secondary hyperlipidemia or dyslipidemia. An LDL receptor abnormality is the most common cause.

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A 47-year-old woman has a tumor that is causing symptoms of excessive hormone production. Surgical resection of the lesion is performed with no operative complications, and the neoplastic tissue is subjected to detailed pathologic studies. Electron microscopy reveals the tumor cells have highly developed, smooth endoplasmic reticulum. Which of the following is a possible direct effect of the substance secreted by these cells?

A. Increase in water reabsorption in the renal collecting ducts
B. Induction of hypoglycemia with increased cellular glucose uptake
C. Promotion of male-pattern hair growth and virilization
D. Stimulation of acid secretion from the gastric parietal cells
E. Stimulation of milk production by the mammary tissue

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A. ~~Increase in water reabsorption in the renal collecting ducts~~ (8%)

B. ~~Induction of hypoglycemia with increased cellular glucose uptake~~ (10%)

✓ C. Promotion of male-pattern hair growth and virilization (63%)

D. ~~Stimulation of acid secretion from the gastric parietal cells~~ (3%)

E. ~~Stimulation of milk production by the mammary tissue~~ (12%)

Correct

63% Answered correctly

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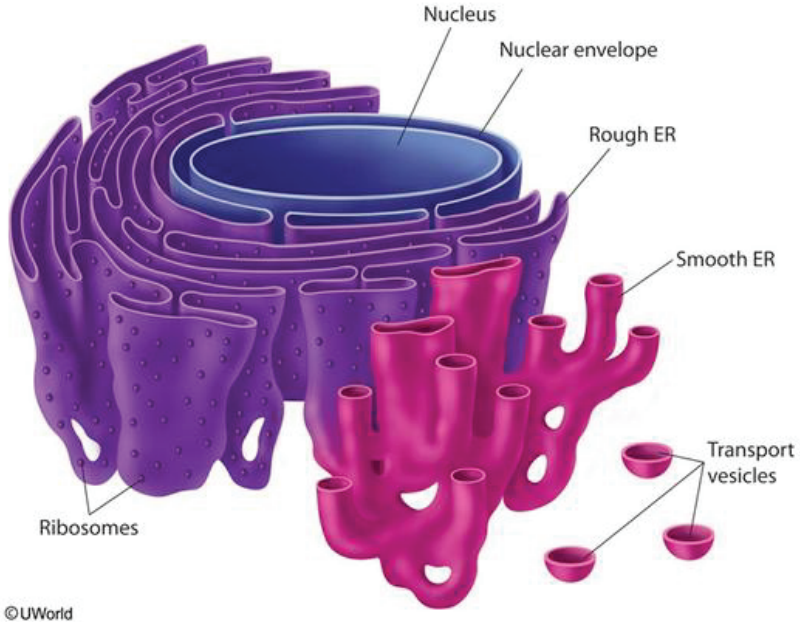
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Rough & smooth endoplasmic reticulum



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The endoplasmic reticulum (ER) is an interconnected, membrane-bound network found in almost all eukaryotic cells. It is highly metabolically active and plays a significant role in the synthesis and modification of cellular components. The ER is recognizable on electron microscopy as a flattened tubular or laminar structure near or adjacent to the nucleus.

The **smooth endoplasmic reticulum** (SER) is involved in the synthesis and processing of hydrophobic compounds, including lipids, phospholipids, and cholesterol derivatives (eg, **steroid hormones**). Cholesterol is initially converted to pregnenolone in the mitochondria and then transferred to the SER, where the remaining steps of steroidogenesis occur. The SER contains the enzymes (eg, 21-hydroxylase) required for steroid and phospholipid biosynthesis. Steroid-producing cells (in the adrenals, gonads, and liver) characteristically contain a well-developed SER. This patient is likely experiencing **virilization** due to an **androgen-secreting** ovarian or adrenal **tumor**. Paraneoplastic syndromes can also occur due to overproduction of other sex steroids, cortisol (ie, Cushing syndrome), or aldosterone.

By contrast, the rough endoplasmic reticulum (RER) is characterized by numerous ribosomes on the outer membrane. The RER plays an important role in the synthesis and modification of targeted proteins, including secretable polypeptide hormones. Some of the clinically significant syndromes due to overproduction of **peptide hormones** by the RER include:

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- Syndrome of inappropriate antidiuretic hormone (characterized by increased water reabsorption in the renal collecting ducts), often abbreviated SIADH, due to overproduction of vasopressin **(Choice A)**
- Hypoglycemia due to overproduction of insulin by certain pancreatic neuroendocrine tumors (insulinomas) **(Choice B)**
- Zollinger-Ellison syndrome (gastric acid hypersecretion and recurrent peptic ulcer) due to excess secretion of gastrin from pancreatic or small intestine gastrinomas **(Choice D)**
- Galactorrhea (pathologic mammary milk production) due to a prolactin-secreting lactotroph pituitary adenoma **(Choice E)**

Educational objective:

The initial step in the synthesis of steroid hormones is the conversion of cholesterol to pregnenolone in the mitochondria. The remainder of steroidogenesis occurs in the smooth endoplasmic reticulum. Steroid-producing cells contain a well-developed smooth endoplasmic reticulum.

References

- The endoplasmic reticulum: structure, function and response to cellular signaling.

Biochemistry | Endocrine, Diabetes & Metabolism | Steroid hormones

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A group of investigators is studying the mechanisms of signal transduction involved in the pathogenesis of type 2 diabetes mellitus. Their research focuses on the intracellular signaling cascade that begins when insulin binds to the insulin receptor. In a series of experiments, they demonstrate that pre-treatment with tumor necrosis factor alpha (TNF-α) results in decreased insulin-mediated glucose uptake. This effect of TNF-α is most likely mediated through upregulation of which of the following processes?

A. Cyclic AMP hydrolyzation
B. Phosphatidylinositol cleavage
C. Proline residue hydroxylation
D. Serine residue phosphorylation
E. Stimulation of peroxisome proliferator-activated receptor

Submit

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A. Cyclic AMP hydrolyzation (25%)
B. Phosphatidylinositol cleavage (18%)
C. Proline residue hydroxylation (4%)
✓ D. Serine residue phosphorylation (31%)
E. Stimulation of peroxisome proliferator-activated receptor (19%)

Correct

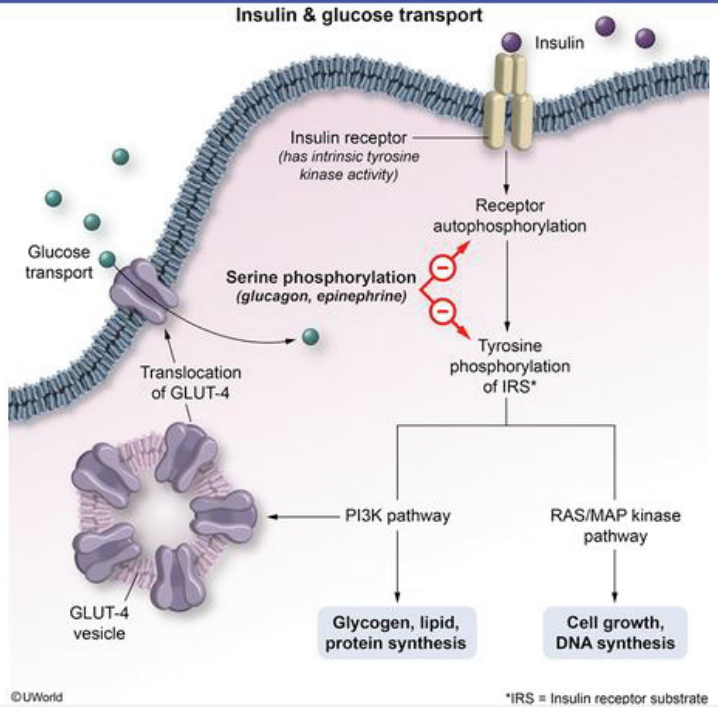
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*IRS = Insulin receptor substrate

The **insulin receptor** (IR) is a tetrameric structure consisting of 2 alpha and 2 beta subunits. The alpha subunits are extracellular and provide the binding site for insulin. The beta subunits are intracellular and contain **tyrosine kinase** domains that are activated when insulin attaches to the alpha subunits. A series of downstream signaling is then triggered, starting with the autophosphorylation of IR, phosphorylation of IR substrates 1 and 2 (IRS-1/2), and ultimately, translocation of glucose transporter-4 (GLUT-4) to the cell membrane.

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that induces insulin resistance through the activation of **serine kinases**, which then phosphorylate serine residues on the beta subunits of IR and IRS-1. This inhibits tyrosine phosphorylation of IRS-1 by IR and subsequently hinders downstream signaling, resulting in resistance to the normal actions of insulin. Phosphorylation of threonine residues has similar effects. Catecholamines, glucocorticoids, and glucagon can also induce insulin resistance by this same mechanism.

(Choice A) Cyclic AMP (cAMP) is inactivated via hydrolysis by phosphodiesterase. Phosphodiesterase can thereby dampen the effects of various hormones (eg, glucagon) that use cAMP as a second messenger. cAMP is also involved in insulin release by pancreatic beta cells, but it does not participate in IR downstream signaling.

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IR downstream signaling.

(Choice B) Some hormones (eg, angiotensin II, gonadotropin-releasing hormone) act on transmembrane receptors coupled with a G_q-protein that activates phospholipase C, which then cleaves phosphatidylinositol biphosphate into two important secondary messengers: inositol triphosphate and diacylglycerol (DAG). Inositol triphosphate mediates its action by increasing intracellular calcium influx, and DAG activates protein kinase C.

(Choice C) Hydroxyproline, a major component of bone and skin collagen, is formed by the hydroxylation of proline, which requires vitamin C. Insulin plays no role in the hydroxylation of proline.

(Choice E) Peroxisome proliferator-activated receptor-gamma (PPAR-γ) alters gene transcription by binding to the promoter region of target genes. Activation of PPAR-γ results in improved insulin sensitivity.

Educational objective:
Phosphorylation of serine and threonine residues of insulin receptor and insulin receptor substrate by serine kinase leads to insulin resistance. This type of phosphorylation can be induced by TNF-α, catecholamines, glucocorticoids, and glucagon.

References

- Insulin resistance induced by tumor necrosis factor-alpha in myocytes and brown adipocytes.

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A 44-year-old man comes to the office for follow-up of type 2 diabetes mellitus. He was diagnosed with diabetes 4 years ago and has been taking metformin since then. Six months ago, a new antidiabetic agent was added due to suboptimal glycemic control. Today, the patient is happy because he has lost 7 kg (15.4 lb) without any changes in diet or activity since the new therapy was started. His only symptoms are occasional nausea, vomiting, and a prolonged sensation of fullness after eating. Vital signs are within normal limits with no orthostatic changes. BMI is 34 kg/m^2. Physical examination shows normal heart and lung sounds, a nontender abdomen, and normal deep tendon reflexes and sensory examination. Laboratory testing reveals normal renal function studies and hemoglobin A1c of 7.2%. If this patient's weight loss is due to the new medication, which of the following agents is most likely responsible?

A. Basal-bolus insulin therapy
B. Dipeptidyl peptidase-4 inhibitor
C. Glucagon-like peptide-1 agonist
D. Sulfonylurea
E. Thiazolidinedione

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A. ~~Basal-bolus insulin therapy~~ (3%)
B. Dipeptidyl peptidase-4 inhibitor (17%)
✓ C. Glucagon-like peptide-1 agonist (59%)
D. ~~Sulfonylurea~~ (9%)
E. Thiazolidinedione (9%)

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Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss

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• Pioglitazone	resistance	failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** =

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• Dapagliflozin		• Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; K_{ATP} = ATP-sensitive potassium; **PPAR-γ** = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.

This patient with uncontrolled diabetes on metformin therapy was started on a second medication to improve his glycemic control. The new agent was associated with significant **weight loss**, a side effect that is characteristic of **glucagon-like peptide-1 (GLP-1) agonists** (eg, exenatide, liraglutide).

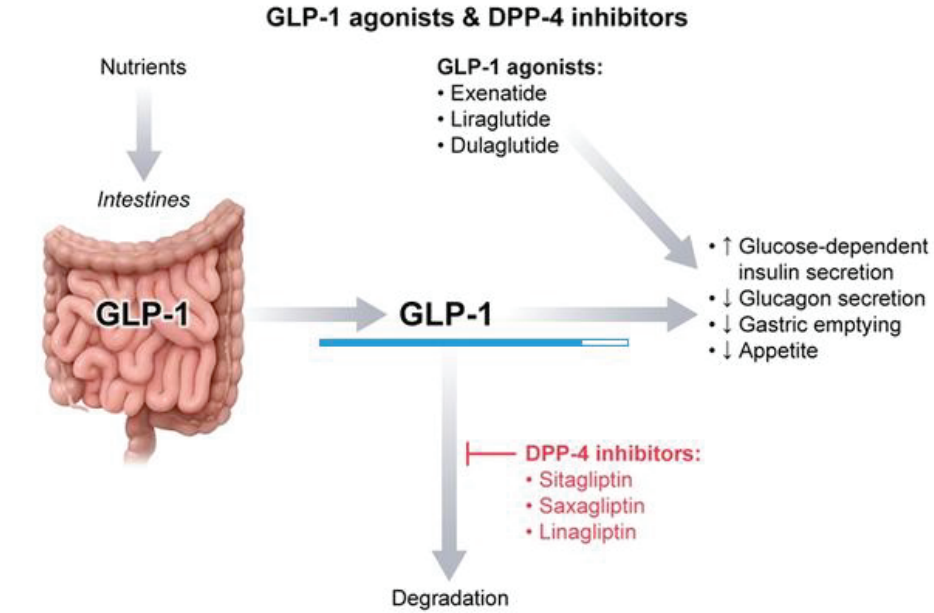
GLP-1 is secreted by intestinal L cells in response to food intake and regulates glucose by slowing gastric emptying, suppressing glucagon secretion, and **increasing glucose-dependent insulin release**. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4), but synthetic GLP-1 agonists are resistant to degradation, allowing for a prolonged therapeutic effect.

Although insulin secretion is increased by GLP-1 agonists, most patients lose weight due to **enhanced satiety** and a **prolonged feeling of fullness** following meals; this effect is also seen in patients who do not have diabetes. GLP-1 agonists are administered parenterally. Adverse effects include nausea and

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satiety and a **prolonged feeling of fullness** following meals; this effect is also seen in patients who do not have diabetes. GLP-1 agonists are administered parenterally. Adverse effects include nausea and vomiting (due to delayed gastric emptying) and pancreatitis, but the risk of hypoglycemia is low because insulin secretion is not stimulated when circulating glucose levels are normal.

(Choice A) Basal-bolus insulin therapy is effective in patients with even the most poorly controlled diabetes (eg, hemoglobin A1c >10%). It has few side effects but is typically associated with significant weight gain.

(Choice B) DPP-4 inhibitors (eg, sitagliptin) are oral agents that block degradation of endogenous GLP-1. They share several side effects with GLP-1 agonists (eg, nausea), but are generally less potent and typically do not induce noticeable weight loss.

(Choice D) Sulfonylureas directly stimulate pancreatic insulin secretion independent of circulating glucose levels. They typically cause weight gain and carry a risk of hypoglycemia.

(Choice E) Thiazolidinediones (eg, pioglitazone) are peroxisome proliferator–activated receptor-gamma agonists that increase transcription of certain insulin-responsive genes and decrease insulin resistance. Because they do not promote insulin release, they do not cause hypoglycemia, but common side effects include fluid retention and weight gain.

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typically do not induce noticeable weight loss.

(Choice D) Sulfonylureas directly stimulate pancreatic insulin secretion independent of circulating glucose levels. They typically cause weight gain and carry a risk of hypoglycemia.

(Choice E) Thiazolidinediones (eg, pioglitazone) are peroxisome proliferator–activated receptor-gamma agonists that increase transcription of certain insulin-responsive genes and decrease insulin resistance. Because they do not promote insulin release, they do not cause hypoglycemia, but common side effects include fluid retention and weight gain.

Educational objective:

Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose levels by slowing gastric emptying, suppressing glucagon secretion, and increasing glucose-dependent insulin release. GLP-1 agonists are parenteral antidiabetic agents that can improve glycemic control with low risk of hypoglycemia. They are also associated with significant weight loss unlike many other antidiabetic agents.

References

- GLP-1 receptor agonists: nonglycemic clinical effects in weight loss and beyond.

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A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

A. ApoC-2 production

B. Cholesterol esterification in the blood

C. Chylomicron remnant uptake by liver cells

D. LDL particle uptake by hepatocytes

E. Lipoprotein lipase activity

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A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

A. ApoC-2 production (1%)
B. Cholesterol esterification in the blood (7%)
✓ C. Chylomicron remnant uptake by liver cells (41%)
D. LDL particle uptake by hepatocytes (35%)
E. Lipoprotein lipase activity (13%)

Correct

41%
Answered correctly

01 min, 26 secs
Time Spent

01/18/2021
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Important inherited hyperlipoproteinemias

Dyslipidemia	Protein defect	Elevated lipoproteins	Major manifestations
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	Chylomicrons	• **Acute pancreatitis** • Lipemia retinalis • Eruptive xanthomas
Familial hypercholesterolemia (type II A)	• LDL receptor • ApoB-100	**LDL**	• **Premature atherosclerosis** • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (type III)	• ApoE	Chylomicron & VLDL remnants	• **Premature atherosclerosis** • Tuboeruptive & palmar xanthomas
Familial hypertriglyceridemia (type IV)	• Polygenic	VLDL	• Associated with coronary disease, pancreatitis & diabetes

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Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is characterized by xanthomas and premature coronary and peripheral vascular disease. It is an autosomal recessive disorder that is clinically more severe in patients with other conditions affecting lipoprotein metabolism (eg, diabetes, hypothyroidism).

The primary defects in familial dysbetalipoproteinemia are in **ApoE3 and ApoE4**, apolipoproteins found on the triglyceride-rich lipoproteins (**chylomicrons and VLDLs**) that are responsible for binding hepatic apolipoprotein receptors. Without ApoE3 and ApoE4, the liver cannot efficiently remove chylomicrons and VLDL remnants from the circulation, causing their accumulation in the blood and resultant elevations in **cholesterol and triglyceride** levels.

(Choices A and E) Familial chylomicronemia syndrome is an autosomal recessive disorder characterized by defective lipoprotein lipase activity with increased synthesis and decreased clearance of chylomicron particles (and VLDL to a lesser extent). It can also be due to ApoC2 deficiency because lipoprotein lipase is activated by ApoC2 on chylomicrons and VLDL.

(Choice B) ApoA1 is required for esterification of free cholesterol in HDL particles by lecithin-cholesterol acyltransferase (LCAT). ApoA1 and LCAT deficiencies result in low HDL levels and increased circulating free cholesterol levels.

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is activated by ApoC2 on chylomicrons and VLDL.

(Choice B) ApoA1 is required for esterification of free cholesterol in HDL particles by lecithin-cholesterol acyltransferase (LCAT). ApoA1 and LCAT deficiencies result in low HDL levels and increased circulating free cholesterol levels.

(Choice D) Familial hypercholesterolemia is associated with increased levels of LDL cholesterol. It is caused by defects in the ApoB/E LDL receptor or ApoB-100 ligand, leading to decreased hepatic clearance of LDL.

Educational objective:
Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is an autosomal recessive disorder characterized by elevated cholesterol and triglyceride levels. It is caused by defects in ApoE3 and ApoE4, leading to decreased clearance of chylomicrons and VLDL remnants. Patients can develop eruptive and palmar xanthomas and premature atherosclerosis.

Biochemistry	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

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A 14-year-old boy is brought to the office due to painless nodules on his lips and tongue. The lesions appeared several months ago and have been progressively enlarging. The patient underwent total thyroidectomy 5 years ago following the discovery of a thyroid mass and takes thyroid hormone replacement. On physical examination, the patient is tall and slender with disproportionately long arms and legs. His fingers are also long and thin, and joint laxity is present. Eye examination is normal and oral inspection reveals several small, soft, flesh-colored papules on his lips and tongue. Serum TSH is within normal limits. This patient most likely has which of the following conditions?

A. Ehlers-Danlos syndrome
B. Marfan syndrome
C. Multiple endocrine neoplasia type 1
D. Multiple endocrine neoplasia type 2B
E. Neurofibromatosis type 1
F. Neurofibromatosis type 2

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appeared several months ago and have been progressively enlarging. The patient underwent total thyroidectomy 5 years ago following the discovery of a thyroid mass and takes thyroid hormone replacement. On physical examination, the patient is tall and slender with disproportionately long arms and legs. His fingers are also long and thin, and joint laxity is present. Eye examination is normal and oral inspection reveals several small, soft, flesh-colored papules on his lips and tongue. Serum TSH is within normal limits. This patient most likely has which of the following conditions?

A. Ehlers-Danlos syndrome (4%)
B. Marfan syndrome (6%)
C. Multiple endocrine neoplasia type 1 (1%)
✓ D. Multiple endocrine neoplasia type 2B (83%)
E. Neurofibromatosis type 1 (2%)
F. Neurofibromatosis type 2 (1%)

Correct

83%
Answered correctly

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Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has a **marfanoid habitus**—a tall and slender build with disproportionately long arms, legs, and fingers. The flesh-colored nodules on his lips and tongue are likely **mucosal neuromas**, which are unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total

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This patient has a **marfanoid habitus**—a tall and slender build with disproportionately long arms, legs, and fingers. The flesh-colored nodules on his lips and tongue are likely **mucosal neuromas**, which are unencapsulated, thickened proliferations of neural tissue. This patient also has a history of total thyroidectomy, which was likely due to **medullary thyroid cancer** (MTC). This combination of clinical findings is consistent with **multiple endocrine neoplasia type 2B** (MEN 2B), which is due to an autosomal dominant germ-line mutation in the *RET* proto-oncogene. Other possible manifestations of MEN 2B include pheochromocytoma and intestinal ganglioneuromas (which may cause constipation). The earliest manifestations of the disease often appear in childhood or adolescence. Early recognition of MEN 2B is important as almost all patients develop MTC and prophylactic thyroidectomy can be life-saving.

(Choice A) Ehlers-Danlos syndrome is a heritable connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, tissue fragility, poor wound healing, and easy bruising. There is no known association between Ehlers-Danlos syndrome and thyroid cancer or perioral nodules.

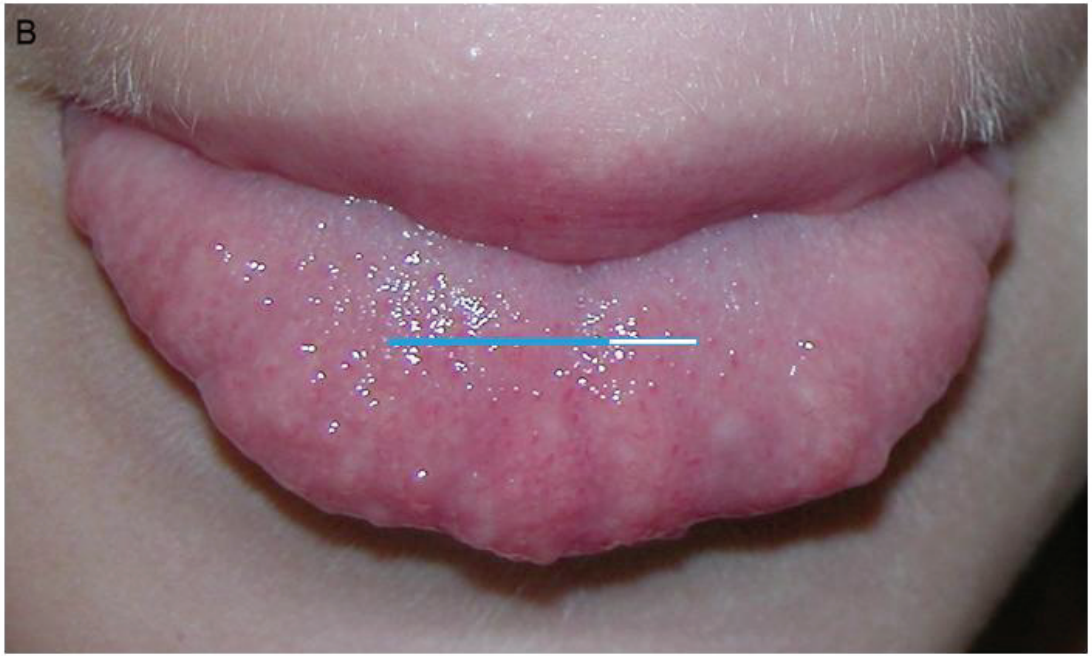
(Choice B) Although this patient has a marfanoid habitus, the remainder of his presentation is more consistent with MEN 2B than Marfan syndrome. In addition, unlike true Marfan syndrome, patients with MEN 2B do not develop aortic malformations (eg, dilation) or ocular malformations (eg, ectopia lentis).

(Choice C) Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant condition characterized

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MEN 2B do not develop aortic malformations (eg, dilation) or ocular malformations (eg, ectopia lentis).

(Choice C) Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant condition characterized by parathyroid adenomas with hyperparathyroidism, anterior pituitary gland tumors, and pancreatic endocrine tumors (the "3 Ps"). MEN 1 is not associated with thyroid cancer or perioral nodules.

(Choices E and F) Neurofibromatosis type 1 is characterized by café au lait spots, cutaneous neurofibromas, axillary or inguinal freckling, optic glioma, and iris hamartomas. Neurofibromatosis type 2 (the more central form) is characterized by bilateral acoustic neuromas, brain meningiomas, and schwannomas of the dorsal roots in the spinal cord. Although this patient has (mucosal) neuromas, the remainder of his presentation is more consistent with MEN 2B.

Educational objective:
Multiple endocrine neoplasia type 2B is characterized by medullary thyroid cancer, pheochromocytoma, marfanoid habitus, and oral and intestinal mucosal neuromas.

References

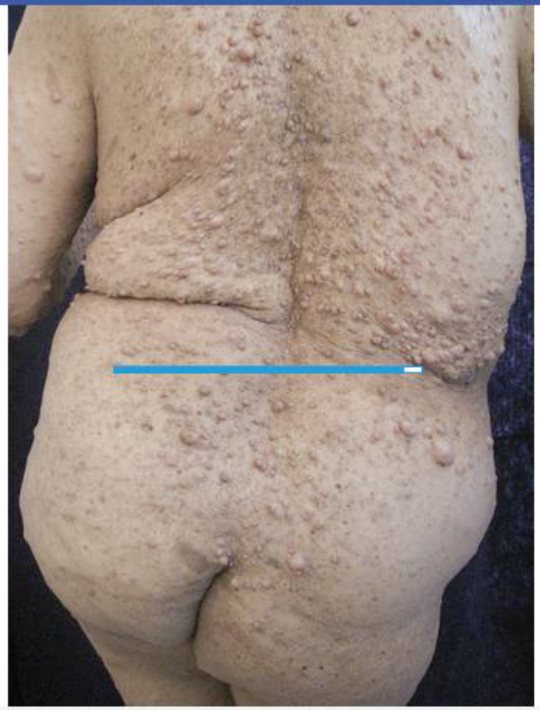
- Multiple endocrine neoplasia type 2: an overview.

Pathology Endocrine, Diabetes & Metabolism Multiple endocrine neoplasia

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Pathology | Endocrine, Diabetes & Metabolism | Multiple endocrine neoplasia

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A 6-year-old boy is brought to the emergency department after a traumatic fall from his bicycle. Physical examination shows a large laceration over his left leg that is irrigated and closed with sutures. While he is receiving care, a routine blood draw shows milky plasma that forms a creamy-appearing supernatant upon standing. Further testing shows that his plasma lipoprotein lipase activity measured after intravenous heparin administration is substantially lower than normal. If his condition remains untreated, this patient is most likely to develop which of the following features?

A. Acute pancreatitis
B. Intellectual disability
C. Myocardial infarction
D. Tendon xanthomas
E. Xanthelasmas

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A 6-year-old boy is brought to the emergency department after a traumatic fall from his bicycle. Physical examination shows a large laceration over his left leg that is irrigated and closed with sutures. While he is receiving care, a routine blood draw shows milky plasma that forms a creamy-appearing supernatant upon standing. Further testing shows that his plasma lipoprotein lipase activity measured after intravenous heparin administration is substantially lower than normal. If his condition remains untreated, this patient is most likely to develop which of the following features?

- A. Acute pancreatitis (38%) ✓
- B. Intellectual disability (1%)
- C. Myocardial infarction (20%)
- D. Tendon xanthomas (24%)
- E. Xanthelasmas (14%)

Correct

38% Answered correctly

43 secs Time Spent

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Important inherited hyperlipoproteinemias

Dyslipidemia	Protein defect	Elevated lipoproteins	Major manifestations
Familial chylomicronemia syndrome (Type I)	• Lipoprotein lipase • ApoC-II	Chylomicrons	• **Acute pancreatitis** • Lipemia retinalis • Eruptive skin xanthomas • Hepatosplenomegaly
Familial hypercholesterolemia (Type II A)	• LDL receptor • ApoB-100	LDL	• **Premature coronary artery disease** • Corneal arcus • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (Type III)	• ApoE	Chylomicron and VLDL remnants	• **Premature coronary artery disease** & peripheral vascular disease • Tuboeruptive &

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syndrome (Type I)	• ApoC-II	Chylomicrons	• Eruptive skin xanthomas • Hepatosplenomegaly
Familial hypercholesterolemia (Type II A)	• LDL receptor • ApoB-100	LDL	• **Premature coronary artery disease** • Corneal arcus • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (Type III)	• ApoE	Chylomicron and VLDL remnants	• **Premature coronary artery disease** & peripheral vascular disease • Tuboeruptive & palmar xanthomas
Familial hypertriglyceridemia (Type IV)	• ApoA-V	VLDL	• Increased pancreatitis risk • Associated with obesity & insulin resistance

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This patient has **familial chylomicronemia syndrome** (type 1 hyperlipoproteinemia), an autosomal recessive condition most often caused by **lipoprotein lipase (LPL) deficiency**. LPL is normally bound to heparan sulfate moieties on the vascular endothelium, allowing it to interact with chylomicrons and VLDL in the circulation and release free fatty acids into the adjacent tissues. Heparin administration releases these endothelium-bound lipases, allowing LPL activity to be measured in the laboratory. Without sufficient LPL activity, the body is unable to clear dietary lipid loads due to defective hydrolysis of serum triglycerides (especially **chylomicrons**).

Patients with familial chylomicronemia syndrome present in childhood with marked **hypertriglyceridemia**, recurrent **acute pancreatitis, lipemia retinalis** (milky-appearing retinal vasculature), and eruptive xanthomas (small yellowish papules surrounded by erythema found mainly on extensor surfaces).

(Choice B) The familial hyperlipoproteinemias are not associated with intellectual disability.

(Choices C, D, and E) Accelerated coronary artery disease, tendon xanthomas (nodular lipid deposits in the tendons, particularly the Achilles), and xanthelasmas are seen in familial hypercholesterolemia, a condition caused by defects in the LDL receptor or its ligand, ApoB-100. As LDL is mainly cleared from the circulation by receptor-mediated uptake in the liver, individuals with familial hypercholesterolemia have dramatically elevated LDL concentrations.

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Patients with familial chylomicronemia syndrome present in childhood with marked **hypertriglyceridemia**, recurrent **acute pancreatitis, lipemia retinalis** (milky-appearing retinal vasculature), and eruptive xanthomas (small yellowish papules surrounded by erythema found mainly on extensor surfaces).

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(Choices C, D, and E) Accelerated coronary artery disease, tendon xanthomas (nodular lipid deposits in the tendons, particularly the Achilles), and xanthelasmas are seen in familial hypercholesterolemia, a condition caused by defects in the LDL receptor or its ligand, ApoB-100. As LDL is mainly cleared from the circulation by receptor-mediated uptake in the liver, individuals with familial hypercholesterolemia have dramatically elevated LDL concentrations.

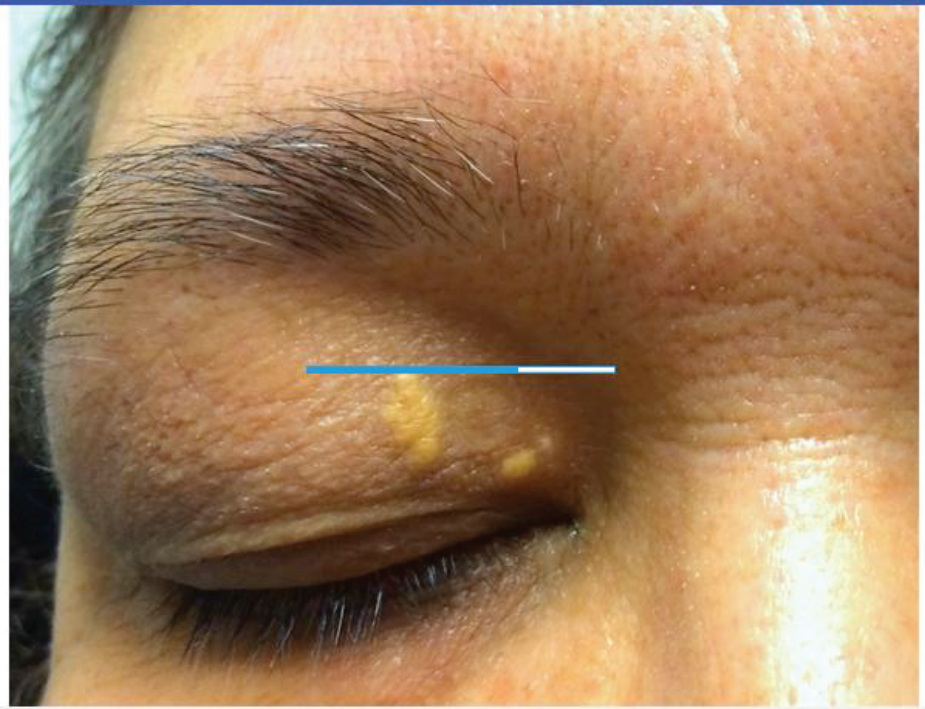
Educational objective:
Familial chylomicronemia syndrome frequently presents in childhood with recurrent episodes of acute pancreatitis. Patients with this disorder are not usually at increased risk for premature coronary artery disease. Eruptive skin xanthomas may be present in hypertriglyceridemia, but tendon xanthomas and xanthelasmas are primarily seen with hypercholesterolemia.

Pathology	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

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Patients with familial chylomicronemia syndrome present in childhood with marked **hypertriglyceridemia**;

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A 48-year-old woman comes to the office for follow-up of primary hypothyroidism due to chronic autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- A. Agranulocytosis
- B. Atrial fibrillation
- C. Dementia
- D. Goiter
- E. Hepatotoxicity
- F. Thyroid cancer

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autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- A. Agranulocytosis (13%)
- ✓ B. Atrial fibrillation (53%)
- C. Dementia (2%)
- D. Goiter (17%)
- E. Hepatotoxicity (8%)
- F. Thyroid cancer (4%)

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Cardiovascular effects of hyperthyroidism	
Increased rate	• Tachycardia/palpitations • Atrial fibrillation
Increased contractility	• ↑ Ejection fraction & cardiac output • ↑ Myocardial oxygen demand & angina • ↑ Pulmonary artery pressure
Decreased afterload	• ↓ Systemic vascular resistance
Additional effects	• ↓ Diastolic pressure • ↑ Systolic pressure • ↑ Pulse pressure • High-output heart failure

This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 µU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased

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This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 µU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting **hyperadrenergic state** can lead to significant cardiovascular complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety,

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(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability). Although hyperthyroidism in elderly patients may manifest as social withdrawal and slowed responses (apathetic depression) resembling dementia, cognitive dysfunction in younger patients is more likely to be seen in hypothyroidism rather than in hyperthyroidism.

(Choice D) The goiter seen in hypothyroidism is due to chronic thyroid stimulation by TSH. This manifestation improves with the administration of levothyroxine (as TSH levels are decreased) and is not seen in over-replacement.

(Choice F) Thyroid cancer is a potential long-term complication of radioiodine therapy for hyperthyroidism.

Educational objective:
Thyrotoxicosis, whether due to endogenous hyperthyroidism or over-replacement with thyroid hormone in patients with hypothyroidism, causes a hyperadrenergic state that can lead to atrial fibrillation, high-output heart failure, and worsening of angina pectoris.

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A 50-year-old man is brought to the emergency department due to a severe, sudden-onset headache that started an hour ago. The patient reports that he has had mild headaches and decreased libido over the past 3 months. He has no other medical conditions and takes no medications. Physical examination reveals bilateral deficits involving the temporal visual fields and impaired extraocular eye movements. Shortly after being admitted to the hospital, he becomes acutely hypotensive and loses consciousness. The patient dies despite aggressive resuscitation efforts. Which of the following is most likely to be found on autopsy?

A. Acute hemorrhage in the pituitary gland
B. Bleeding within the putamen
C. Dissection of the internal carotid artery
D. Inflamed temporal arteries
E. Ischemic necrosis of the pituitary gland
F. Ruptured intracranial aneurysm
G. Thrombus in the venous sinuses

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past 5 months. He has no other medical conditions and takes no medications. Physical examination reveals bilateral deficits involving the temporal visual fields and impaired extraocular eye movements. Shortly after being admitted to the hospital, he becomes acutely hypotensive and loses consciousness. The patient dies despite aggressive resuscitation efforts. Which of the following is most likely to be found on autopsy?

- A. Acute hemorrhage in the pituitary gland (61%)
- B. ~~Bleeding within the putamen~~ (1%)
- C. ~~Dissection of the internal carotid artery~~ (1%)
- D. ~~Inflamed temporal arteries~~ (1%)
- E. Ischemic necrosis of the pituitary gland (12%)
- F. ~~Ruptured intracranial aneurysm~~ (19%)
- G. ~~Thrombus in the venous sinuses~~ (2%)

Correct

61%

01 min, 14 secs

02/05/2021

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Pituitary apoplexy	
Pathogenesis	• Acute pituitary hemorrhage • Usually occurs in preexisting adenoma
Clinical presentation	• Severe headache • Bitemporal hemianopsia (optic chiasm) & ophthalmoplegia (CN III) • Hemodynamic instability & altered sensorium
Complications	• Panhypopituitarism (acute & chronic) • Severe hypotension (central adrenal failure) • Coma & death

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This patient had typical features of acute pituitary hemorrhage (**pituitary apoplexy**), including a severe **headache**, **bitemporal hemianopsia** (due to compression of the optic chiasm), and **ophthalmoplegia** (due to compression of the oculomotor nerve [CN III]). Pituitary apoplexy usually occurs in a preexisting **pituitary adenoma**, as in this patient with chronic headaches and low libido (likely due to hyperprolactinemia). The diagnosis can be confirmed on cross-sectional imaging (CT or MRI scan).

Patients with pituitary apoplexy can develop cardiovascular collapse due to ACTH deficiency and subsequent **adrenocortical insufficiency**. Pituitary apoplexy is a medical emergency that requires urgent neurosurgical consultation and treatment with **glucocorticoids** .

(Choice B) Hemorrhage into the putamen (basal ganglia) causes neurologic deficits that gradually worsen over minutes to hours. Typical features include contralateral hemiparesis and hemianesthesia due to disruption of the corticospinal and somatosensory tracts. It is most often seen in chronic hypertensive vasculopathy.

(Choice C) Carotid dissection typically presents with unilateral headache, transient vision loss, ptosis, and miosis (partial Horner syndrome). It usually occurs following trauma, or can occur spontaneously in patients with chronic hypertension, connective tissue disease, or history of smoking.

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vasculopathy.

(Choice C) Carotid dissection typically presents with unilateral headache, transient vision loss, ptosis, and miosis (partial Horner syndrome). It usually occurs following trauma, or can occur spontaneously in patients with chronic hypertension, connective tissue disease, or history of smoking.

(Choice D) Typical symptoms of giant cell (temporal) arteritis include headaches, jaw claudication, and visual disturbances (eg, amaurosis fugax, anterior ischemic optic neuropathy). Patients frequently also have systemic symptoms (eg, fever, fatigue) and proximal muscle pain (polymyalgia rheumatica).

(Choice E) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary during childbirth. It presents with chronic hypopituitarism (eg, failure to lactate). Severe headaches and visual field defects do not occur.

(Choice F) Rupture of a saccular aneurysm near the optic chiasm can present similarly to pituitary apoplexy. However, this patient's chronic history of decreased libido and acute cardiovascular collapse is more suggestive of a pituitary etiology.

(Choice G) Cerebral venous sinus thrombosis is most common in patients with underlying thrombophilia, pregnancy, oral contraceptive use, malignancy, or infection. Presenting features include headaches, vomiting, seizures, and focal neurologic deficits.

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(Choice E) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary during childbirth. It presents with chronic hypopituitarism (eg, failure to lactate). Severe headaches and visual field defects do not occur.

(Choice F) Rupture of a saccular aneurysm near the optic chiasm can present similarly to pituitary apoplexy. However, this patient's chronic history of decreased libido and acute cardiovascular collapse is more suggestive of a pituitary etiology.

(Choice G) Cerebral venous sinus thrombosis is most common in patients with underlying thrombophilia, pregnancy, oral contraceptive use, malignancy, or infection. Presenting features include headaches, vomiting, seizures, and focal neurologic deficits.

Educational objective:

Acute pituitary hemorrhage (pituitary apoplexy) is characterized by severe headaches, bitemporal hemianopsia (compression of the optic chiasm), and ophthalmoplegia (compression of the oculomotor nerve). It usually occurs in a preexisting pituitary adenoma. Pituitary apoplexy is a medical emergency that requires urgent treatment with glucocorticoids to prevent acute adrenal crisis and circulatory collapse.

References

- Pituitary apoplexy: pathophysiology, diagnosis and management.

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A 46-year-old woman comes to the office for follow-up. Six months ago, the patient underwent total thyroidectomy followed by radioactive iodine ablation for invasive follicular thyroid cancer with distant metastasis. After surgery, she was prescribed levothyroxine to prevent thyroid cancer regrowth. Over the past 4 months, the patient has had a 4.5-kg (10 lb) unintentional weight loss despite having a normal appetite. She also feels unusually hot and sweaty. Temperature is 37 C (98.6 F), blood pressure is 150/70 mm Hg, pulse is 110/min, and respirations are 17/min. Examination reveals a fine hand tremor and sweaty palms. Serum thyroid function testing would most likely reveal which of the following?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
A.	Decreased	Increased	Increased
B.	Decreased	Decreased	Increased
C.	Decreased	Normal	Normal
D.	Decreased	Normal	Decreased
E.	Increased	Increased	Increased

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	TSH	Thyroxine (T4)	Triiodothyronine (T3)
A.	Decreased	Increased	Increased
B.	Decreased	Decreased	Increased
C.	Decreased	Normal	Normal
D.	Decreased	Normal	Decreased
E.	Increased	Increased	Increased
F.	Decreased	Increased	Decreased

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past 4 months, the patient has had a 4.5-kg (10 lb) unintentional weight loss despite having a normal appetite. She also feels unusually hot and sweaty. Temperature is 37 C (98.6 F), blood pressure is 150/70 mm Hg, pulse is 110/min, and respirations are 17/min. Examination reveals a fine hand tremor and sweaty palms. Serum thyroid function testing would most likely reveal which of the following?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)	
✓ A.	Decreased	Increased	Increased	(74%)
B.	Decreased	Decreased	Increased	(10%)
C.	Decreased	Normal	Normal	(1%)
D.	Decreased	Normal	Decreased	(0%)
E.	~~Increased~~	~~Increased~~	~~Increased~~	(2%)
F.	Decreased	Increased	Decreased	(10%)

74%
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09/18/2020

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Exogenous thyrotoxicosis	
Causes	• Thyroid replacement dosing error • Levothyroxine suppression of thyroid cancer • Nonprescribed thyroid hormone use (eg, factitious disorder, weight-loss supplements)
Laboratory markers	• Elevated T3 and thyroxine levels* • Suppressed TSH • Low serum thyroglobulin • Low radioiodine uptake

*Use of T3 supplement (liothyronine) shows elevated T3 only.

T3 = triiodothyronine.

This patient has **thyrotoxicosis** (eg, weight loss, tremor, tachycardia) due to suppressive-dose levothyroxine therapy. Because TSH can promote growth of residual malignant cells following thyroidectomy, patients with **thyroid cancer** at high risk of recurrence (eg, known metastasis) are often prescribed levothyroxine doses that are higher than what is needed for simple replacement. These

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Causes	• Thyroid replacement dosing error • Levothyroxine suppression of thyroid cancer • Nonprescribed thyroid hormone use (eg, factitious disorder, weight-loss supplements)
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This patient has **thyrotoxicosis** (eg, weight loss, tremor, tachycardia) due to suppressive-dose levothyroxine therapy. Because TSH can promote growth of residual malignant cells following thyroidectomy, patients with **thyroid cancer** at high risk of recurrence (eg, known metastasis) are often prescribed levothyroxine doses that are higher than what is needed for simple replacement. These

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T3 = triiodothyronine.

This patient has **thyrotoxicosis** (eg, weight loss, tremor, tachycardia) due to suppressive-dose levothyroxine therapy. Because TSH can promote growth of residual malignant cells following thyroidectomy, patients with **thyroid cancer** at high risk of recurrence (eg, known metastasis) are often prescribed **levothyroxine** doses that are **higher** than what is needed for simple replacement. These higher doses adequately **suppress pituitary secretion of TSH**, however, they can also can cause symptomatic thyrotoxicosis.

When exogenous thyrotoxicosis is due to levothyroxine or mixed T3/T4 supplements (eg, porcine thyroid extract), **total and free thyroxine (T4) levels are elevated**; triiodothyronine (T3) is produced primarily by deiodination of T4 in peripheral tissues, so **T3 levels also are elevated**, even if the patient is taking levothyroxine only **(Choice F)**. In contrast, thyrotoxicosis due to the intake of liothyronine (exogenous T3) is associated with high serum T3 and low T4 **(Choice B)**.

(Choice C) Subclinical hyperthyroidism is characterized by a mildly suppressed TSH with normal thyroid hormone levels. Patients with subclinical hyperthyroidism are typically asymptomatic. This patient takes suppressive-dose levothyroxine to manage metastatic thyroid cancer and has overt hyperthyroid symptoms; thyroid hormone levels are likely to be elevated.

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hormone levels. Patients with subclinical hyperthyroidism are typically asymptomatic. This patient takes suppressive-dose levothyroxine to manage metastatic thyroid cancer and has overt hyperthyroid symptoms; thyroid hormone levels are likely to be elevated.

(Choice D) Patients with severe, acute illness may develop thyroid function abnormalities resembling a mild central hypothyroid state, with low TSH, normal T4, and low T3 (ie, euthyroid sick syndrome). Patients receiving suppressive-dose levothyroxine typically have normal or elevated T3 due to peripheral deiodination.

(Choice E) Central/secondary hyperthyroidism (eg, TSH-secreting pituitary adenoma) is characterized by elevated TSH and thyroid hormone levels. Patients receiving suppressive-dose levothyroxine have low TSH due to feedback inhibition of TSH release.

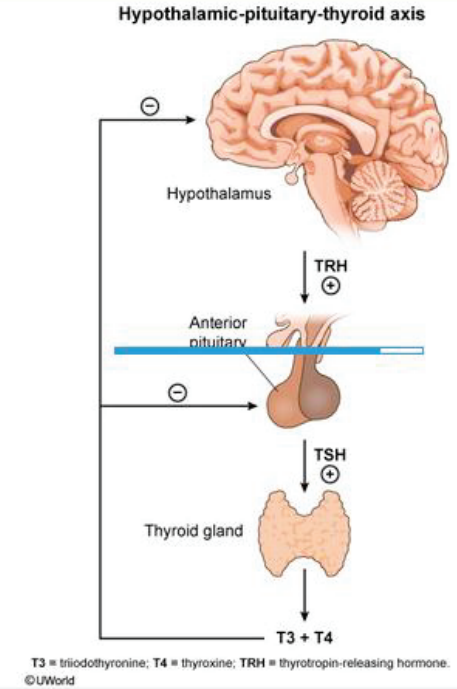
Educational objective:
Exogenous thyrotoxicosis can be caused by suppressive levothyroxine therapy for thyroid cancer. When exogenous thyrotoxicosis is due to levothyroxine or mixed T3/T4 supplements, thyroxine (T4) levels are elevated; triiodothyronine (T3) is produced primarily by the peripheral deiodination of T4, so T3 levels also are elevated even if the patient is taking T4 only.

Physiology Endocrine, Diabetes & Metabolism Hyperthyroidism

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hormone levels. Patients with subclinical hyperthyroidism are typically asymptomatic. This patient takes

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Physiology | Endocrine, Diabetes & Metabolism | Hyperthyroidism

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A 66-year-old man comes to the office to discuss his sexual health. He thinks that he has symptoms of low testosterone, similar to those described in an article he recently read in a health magazine. The patient has normal sexual desire but reduced spontaneous erections and reduced semen volume with ejaculation. He requires more stimulation to achieve a satisfactory erection and has a longer sexual refractory period than before. The patient has no known medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs are normal. BMI is 24.5 kg/m^2. Physical examination, including examination of the testes, is normal. After laboratory testing is completed, the physician finds no evidence of organic disease and concludes that the results are consistent with normal aging. Compared to a healthy young man, which of the following sets of test results would be most consistent with the physician's conclusion?

	Total testosterone	Free testosterone	Sex hormone–binding globulin
A.	Decreased	Decreased	Increased
B.	Decreased	Increased	Unchanged

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alcohol, or illicit drugs. Vital signs are normal. BMI is 24.5 kg/m². Physical examination, including examination of the testes, is normal. After laboratory testing is completed, the physician finds no evidence of organic disease and concludes that the results are consistent with normal aging. Compared to a healthy young man, which of the following sets of test results would be most consistent with the physician's conclusion?

	Total testosterone	Free testosterone	Sex hormone–binding globulin
A.	Decreased	Decreased	Increased
B.	Decreased	Increased	Unchanged
C.	Decreased	Unchanged	Decreased
D.	Increased	Increased	Decreased
E.	Increased	Unchanged	Increased

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examination of the testes, is normal. After laboratory testing is completed, the physician finds no evidence of organic disease and concludes that the results are consistent with normal aging. Compared to a healthy young man, which of the following sets of test results would be most consistent with the physician's conclusion?

	Total testosterone	Free testosterone	Sex hormone–binding globulin	
✓ A.	Decreased	Decreased	Increased	(56%)
B.	~~Decreased~~	~~Increased~~	~~Unchanged~~	(3%)
C.	Decreased	Unchanged	Decreased	(36%)
D.	~~Increased~~	~~Increased~~	~~Decreased~~	(1%)
E.	~~Increased~~	~~Unchanged~~	~~Increased~~	(2%)

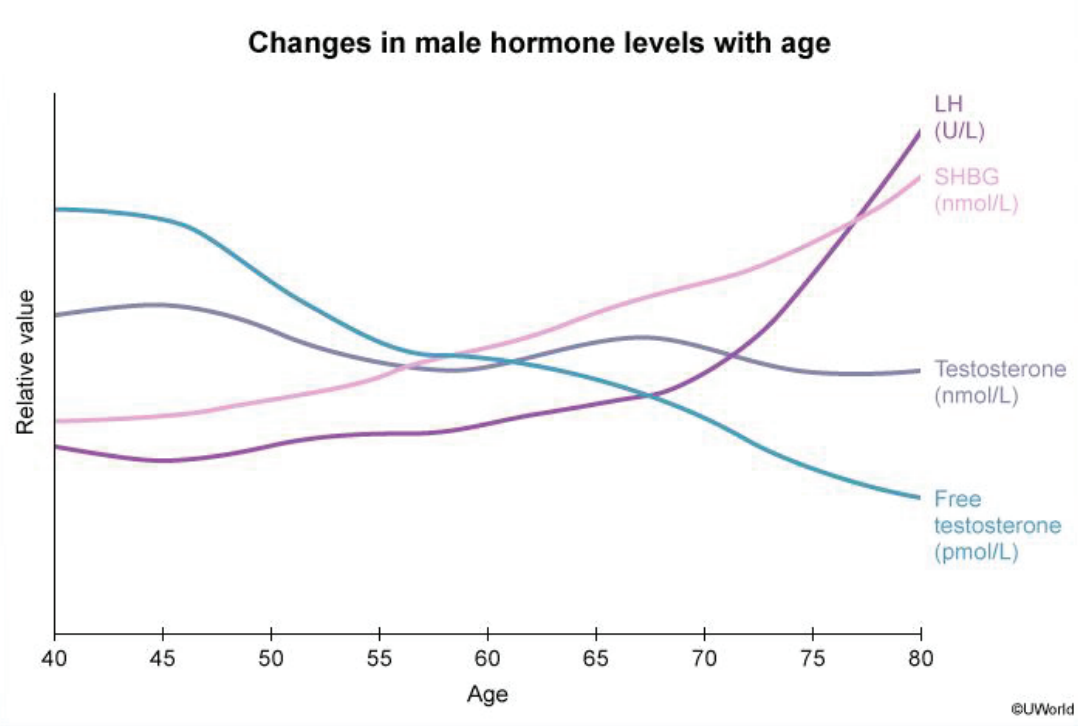
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Unlike women, who typically experience a precipitous drop in sex hormone levels at menopause, men generally experience slower, more variable declines with aging. Typical findings seen in **normal aging**

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Age

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Unlike women, who typically experience a precipitous drop in sex hormone levels at menopause, men generally experience slower, more variable declines with aging. Typical findings seen in **normal aging** include the following:

- Slow decline in gonadal testosterone production with **lower total and free testosterone levels**
- A compensatory **rise in circulating LH levels**
- **Increased** hepatic synthesis (and rising serum levels) of **sex hormone–binding globulin** (SHBG)

Compared to women of similar age, men often report higher levels of sexual functioning, activity, and satisfaction as they age. However, men commonly experience mild, nonspecific changes in sexual function, including the following:

- **Decreased ejaculate volume**
- **Increased erectile latency** and sexual refractory period (ie, time from orgasm until another orgasm is possible)
- Moderately **impaired erectile function** with increased stimulation needed to achieve an erection

At very advanced age (eg, >80), very low testosterone levels can lead to specific hypogonadal symptoms

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- Moderately **impaired erectile function** with increased stimulation needed to achieve an erection

At very advanced age (eg, >80), very low testosterone levels can lead to specific hypogonadal symptoms (eg, loss of libido, erectile failure). However, this patient has nonspecific symptoms that are common in aging and do not suggest underlying gonadal failure.

(Choice B) Certain synthetic androgen analogues (eg, danazol) and progestins (eg, levonorgestrel) can displace testosterone from SHBG, increasing free testosterone without a significant change in SHBG levels. However, this pattern is not seen in normal aging.

(Choice C) SHBG levels are suppressed in patients with insulin resistance, diabetes, and obesity. If the pituitary-gonadal axis is intact, total testosterone levels are reduced, but free testosterone levels are relatively preserved. However, this patient has a normal weight, and SHBG is likely increased at age 66.

(Choice D) Testosterone suppresses SHBG synthesis. Excessive, unregulated testosterone (eg, exogenous androgen abuse) would usually be associated with low SHBG levels, but these values would not be seen in normal aging.

(Choice E) Hyperthyroidism often causes increased production of SHBG independent of age; total testosterone increases to saturate the increased steroid hormone–binding sites, and free testosterone is

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exogenous androgen abuse) would usually be associated with low SHBG levels, but these values would not be seen in normal aging.

(Choice E) Hyperthyroidism often causes increased production of SHBG independent of age; total testosterone increases to saturate the increased steroid hormone–binding sites, and free testosterone is unchanged. Although this patient likely has increased SHBG levels, his total and free testosterone levels are more likely decreased due to the effects of aging.

Educational objective:

Normal aging in men is associated with a slow decline in gonadal testosterone production, a compensatory rise in LH, and rising serum levels of sex hormone–binding globulin. Common, nonspecific symptoms include decreased ejaculate volume, increased erectile latency and sexual refractory time, and moderately impaired erectile function.

References

- Endocrinology of the aging male.

Physiology	Endocrine, Diabetes & Metabolism	Aging
Subject	System	Topic

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A 65-year-old man with benign prostatic hyperplasia comes to the office for a follow-up appointment. He has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following effects?

A. Blockade of androgen receptors
B. Decreased testicular production of testosterone
C. Displacement of estrogen from sex hormone–binding globulin
D. Increased peripheral conversion of testosterone to estrone
E. Increased prolactin production

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has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following effects?

A. ~~Blockade of androgen receptors~~ (27%)

B. ~~Decreased testicular production of testosterone~~ (9%)

C. ~~Displacement of estrogen from sex hormone–binding globulin~~ (4%)

D. Increased peripheral conversion of testosterone to estrone (54%)

E. Increased prolactin production (3%)

Correct

54%

01 min, 19 secs

08/30/2020

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Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis
Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity) • Decreased testosterone levels (eg, chronic kidney disease, hypogonadism) • Medication effect ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole) ◦ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors) ◦ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

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- Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone** (which has a higher affinity for the testosterone receptor and mediates the majority of testosterone effects); the **excess testosterone** is then **converted to estrogens** (eg, estrone) by aromatase, leading to gynecomastia. Both the beneficial effects and potential gynecomastia develop slowly and are generally not apparent in the first several months of therapy with 5-alpha reductase inhibitors.

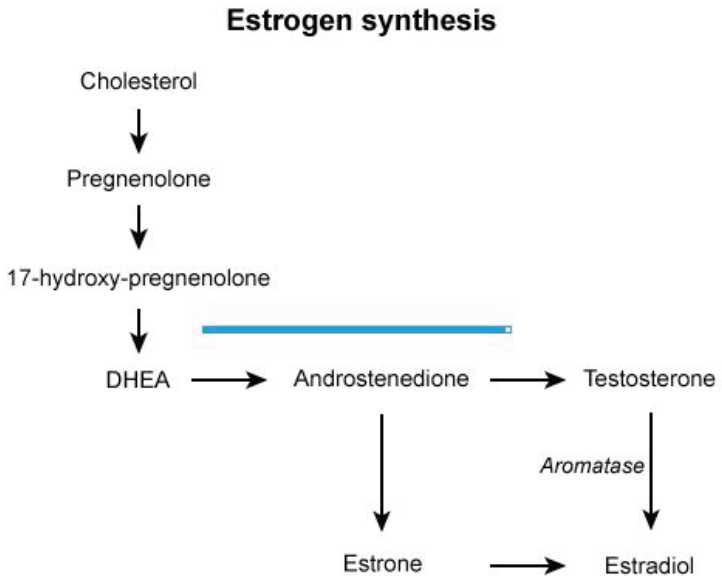
(Choice A) Cimetidine, spironolactone, and antiandrogens (eg, flutamide, bicalutamide) block the binding of androgens to receptors in target tissues.

(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH

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- Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

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(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH analogues (eg, leuprolide) suppress LH secretion and also decrease testicular testosterone production (in contrast with endogenous [pulsatile] GnRH secretion).

(Choice C) Multiple medications, including spironolactone and ketoconazole, can displace estrogen from plasma binding proteins and raise free estrogen levels.

(Choice E) Pituitary prolactin secretion is under negative regulation by dopamine. Dopamine receptor antagonists (eg, antipsychotic medications) facilitate increased prolactin release and can cause a sense of fullness in the breasts and occasionally galactorrhea.

Educational objective:

5-Alpha reductase inhibitors (eg, finasteride, dutasteride) are used in the treatment of benign prostatic hyperplasia. These medications block the conversion of testosterone to dihydrotestosterone; the excess testosterone is then available for conversion to estrogens (eg, estradiol) by aromatase, which can lead to gynecomastia.

References

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A 26-year-old man comes to the emergency department due to a 10-hour history of progressively worsening right-sided scrotal pain. Clinical and radiological evaluations confirm testicular torsion with significant ischemic damage and the patient undergoes unilateral orchiectomy. Three months later, he comes to the office for follow-up. The patient is otherwise healthy and takes no medications but is worried about the risk of sexual dysfunction and infertility. Further evaluation is most likely to show which of the following sets of findings in this patient?

	Erectile function	Sperm count
A.	Decreased	Decreased
B.	Normal	Decreased
C.	Normal	Normal
D.	Decreased	Normal

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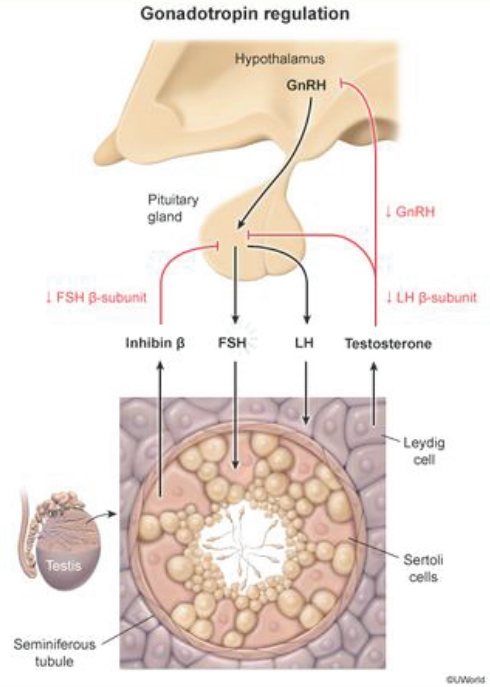
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	Erectile function	Sperm count	
A.	Decreased	Decreased	(1%)
B.	Normal	Decreased	(59%)
C.	Normal	Normal	(38%)
D.	Decreased	Normal	(1%)

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Spermatogenesis in the testis is dependent on 2 primary hormone systems. Testicular Leydig cells produce **testosterone** in response to LH from the pituitary; in turn, LH is regulated by feedback inhibition from testosterone. At the same time, FSH from the pituitary induces the Sertoli cells to produce androgen binding protein (ABP), which concentrates testosterone in the seminiferous tubules and facilitates spermatogenesis. The Sertoli cells also produce inhibin, which provides feedback regulation of FSH.

Following **unilateral orchiectomy**, the initial drop in circulating testosterone stimulates pituitary LH secretion, leading to **compensatory testosterone production** and Leydig cell hyperplasia in the remaining testis. Testosterone levels are quickly restored, maintaining normal libido, erectile function, and secondary sex characteristics.

Concurrently, the loss of inhibin following unilateral orchiectomy leads to increased pituitary FSH release, stimulating ABP production and facilitating spermatogenesis in the remaining testis. However, due to the **loss of seminiferous tubules** in the orchiectomized testis, most patients experience **decreased net spermatogenesis**, often with reduced fertility **(Choice C)**.

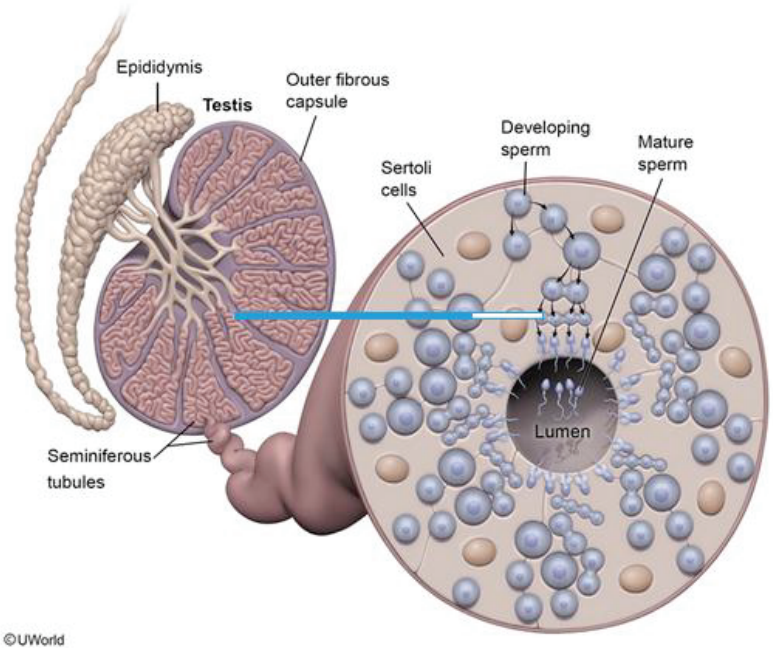
(Choice A) Bilateral testicular damage (eg, orchitis, bilateral orchiectomy) leads to azoospermia. In addition, nontesticular sources of testosterone (eg, adrenals) are often inadequate to maintain normal libido and erectile function.

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Spermatogenesis



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spermatogenesis, often with reduced fertility **(Choice C)**.

(Choice A) Bilateral testicular damage (eg, orchitis, bilateral orchiectomy) leads to azoospermia. In addition, nontesticular sources of testosterone (eg, adrenals) are often inadequate to maintain normal libido and erectile function.

(Choice D) Erectile dysfunction (ED) with normal sperm counts can be caused by a variety of disorders (eg, neurologic or vascular disorders, psychogenic ED), but most patients who have loss of testosterone production severe enough to cause ED will also have impaired spermatogenesis.

Educational objective:
Following unilateral orchiectomy, the drop in testosterone stimulates pituitary LH secretion, which stimulates increased testosterone production in the remaining testis and maintains libido, erectile function, and secondary sex characteristics. However, the loss of sperm-producing tissue usually causes a drop in sperm counts.

Physiology	Endocrine, Diabetes & Metabolism	Male sexual dysfunction
Subject	System	Topic

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A 70-year woman comes to the office due to acute midthoracic back pain that started after a ground-level fall. The patient has also had weakness and weight loss for the past 2 months. Blood pressure is 150/70 mm Hg and pulse is 110/min. Examination shows sweaty palms and a fine hand tremor. Laboratory evaluation reveals normal hemoglobin, serum calcium, serum creatinine, and 25-hydroxyvitamin D levels. Serum thyrotropin (TSH) is undetectable. X-ray reveals a compression fracture of the T7 vertebra with diffuse demineralization of the bones. Which of the following is most likely responsible for the bone abnormalities in this patient?

A. Decreased bone formation due to inhibition of osteoblast differentiation
B. Decreased mineralization of bone matrix
C. Increased bone resorption due to increased calcitonin release
D. Increased bone resorption due to stimulation of osteoclasts
E. Interleukin-1–induced uncoupling of bone resorption and formation

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A 70-year woman comes to the office due to acute midthoracic back pain that started after a ground-level fall. The patient has also had weakness and weight loss for the past 2 months. Blood pressure is 150/70 mm Hg and pulse is 110/min. Examination shows sweaty palms and a fine hand tremor. Laboratory evaluation reveals normal hemoglobin, serum calcium, serum creatinine, and 25-hydroxyvitamin D levels. Serum thyrotropin (TSH) is undetectable. X-ray reveals a compression fracture of the T7 vertebra with diffuse demineralization of the bones. Which of the following is most likely responsible for the bone abnormalities in this patient?

A. ~~Decreased bone formation due to inhibition of osteoblast differentiation~~ (14%)

B. ~~Decreased mineralization of bone matrix~~ (16%)

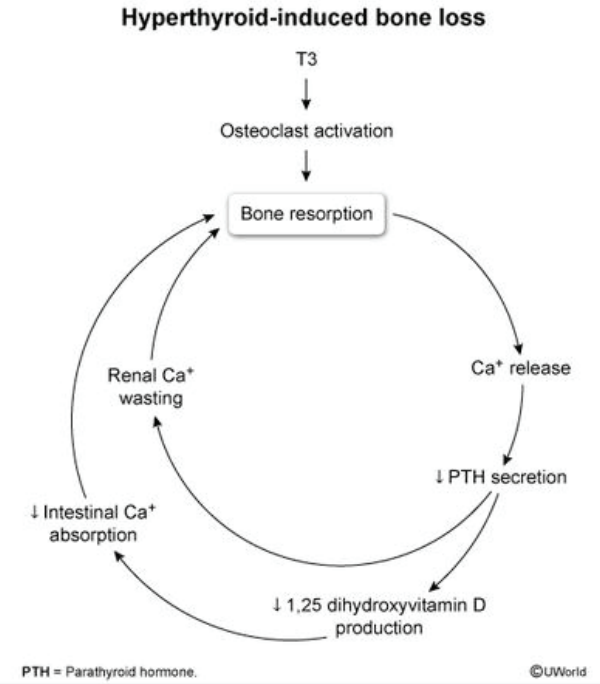
C. ~~Increased bone resorption due to increased calcitonin release~~ (7%)

D. Increased bone resorption due to stimulation of osteoclasts (54%)

E. Interleukin-1–induced uncoupling of bone resorption and formation (7%)

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This patient has **hyperthyroidism**, presenting with weight loss, tremor, tachycardia, and a suppressed TSH level. In addition, she has an acute vertebral compression fracture and diffuse bone mineral loss consistent with **osteoporosis**.

Hyperthyroidism causes increased bone turnover with **net bone loss**. The bone loss in hyperthyroidism is driven by **triiodothyronine (T3)**, the more active form of thyroid hormone that is generated primarily by deiodination of thyroxine (T4) in peripheral tissues. T3 stimulates osteoclast differentiation, **increased bone resorption**, and release of calcium.

As calcium is released from the bones into the circulation, it suppresses parathyroid hormone (PTH) secretion, which leads to decreased reabsorption of calcium in the renal tubules and gut. This maintains **normal blood calcium levels** as bone mineralization is progressively depleted.

(Choice A) Thyroid hormone stimulates (not inhibits) osteoblast differentiation and activity, leading to increased formation of new bone. However, in the hyperthyroid state, this effect is outweighed by a greater increase in bone loss.

(Choice B) Mineralization of bone matrix is regulated directly by local concentrations of calcium and inorganic phosphate and indirectly by multiple endocrine and paracrine factors (eg, PTH, vitamin D). Although vitamin D deficiency can cause osteomalacia due to impaired mineralization, thyroid hormone has

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(Choice B) Mineralization of bone matrix is regulated directly by local concentrations of calcium and inorganic phosphate and indirectly by multiple endocrine and paracrine factors (eg, PTH, vitamin D). Although vitamin D deficiency can cause osteomalacia due to impaired mineralization, thyroid hormone has only a minor effect on this process.

(Choice C) Calcitonin is released by the parafollicular cells of the thyroid. It inhibits osteoclast activity, leading to decreased (not increased) bone resorption. Calcitonin is regulated primarily by circulating calcium levels, not thyroid hormone.

(Choice E) In addition to causing lytic bone lesions, multiple myeloma causes diffuse bone loss due to interleukin-1–induced uncoupling of bone resorption and formation (ie, increased osteoclast activity without a restorative osteoblast action).

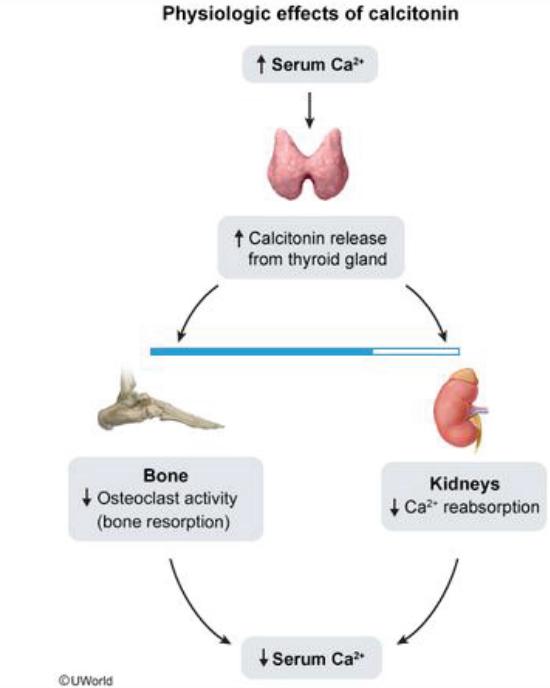
Educational objective:
Hyperthyroidism causes increased bone turnover with net bone loss, potentially leading to osteoporosis. The bone loss is driven by triiodothyronine, which stimulates osteoclast differentiation, increased bone resorption, and release of calcium.

Physiology | Endocrine, Diabetes & Metabolism | Hyperthyroidism

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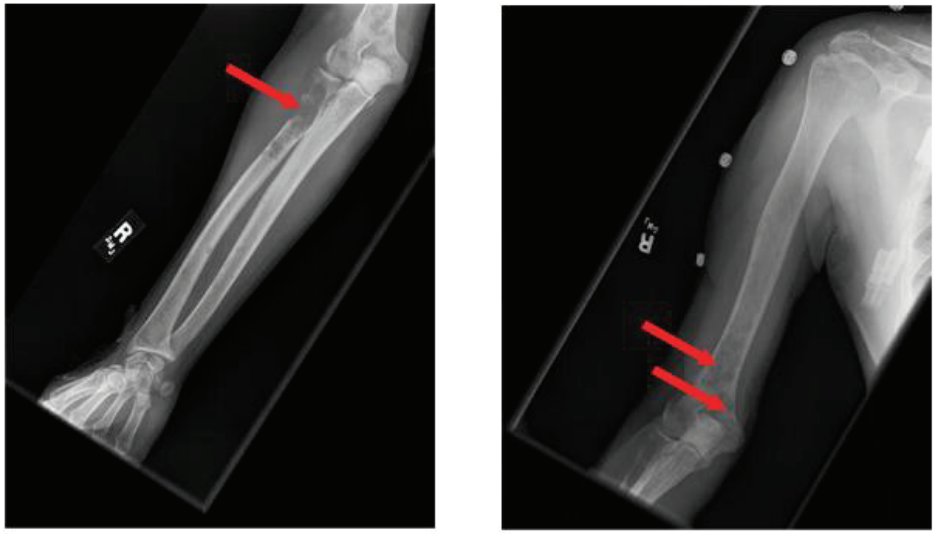
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Osteolytic bony metastases in multiple myeloma

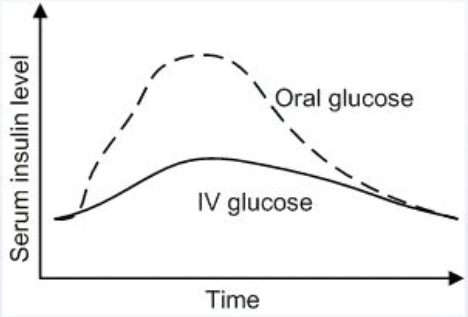


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Researchers measure the serum insulin levels of healthy volunteers after equivalent loads of oral and intravenous glucose. The following curves are observed:

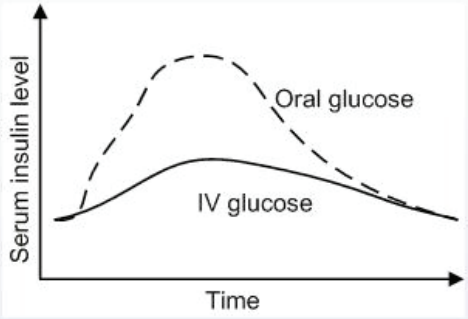


Which of the following endogenous substances best explains the difference between the curves?

A. Insulin-like growth factor-1
B. Glucagon-like peptide-1
C. Somatostatin
D. Secretin

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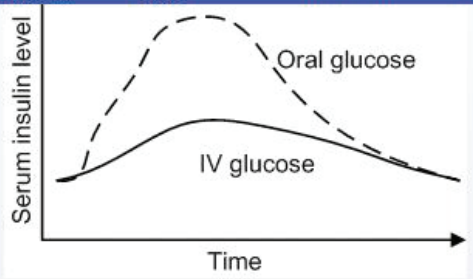
intravenous glucose. The following curves are observed:



Which of the following endogenous substances best explains the difference between the curves?

A. Insulin-like growth factor-1
B. Glucagon-like peptide-1
C. Somatostatin
D. Secretin
E. Cholecystokinin

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Which of the following endogenous substances best explains the difference between the curves?

A. Insulin-like growth factor-1 (19%)
B. Glucagon-like peptide-1 (51%)
C. Somatostatin (10%)
D. Secretin (12%)
E. Cholecystokinin (6%)

Correct

51%

28 secs

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Incretins are gastrointestinal hormones produced by the gut mucosa that stimulate pancreatic insulin secretion in response to sugar-containing meals. This response is independent of blood glucose levels, and typically occurs prior to any elevation in blood glucose level following a meal. Two hormones with incretin effects are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Insulin levels will also increase following intravenous administration of glucose due to the sensitivity of the pancreatic beta-cells to increases in blood glucose, but this increase will not be as marked as that seen following oral glucose administration because the effect of incretin is absent.

(Choice A) Insulin-like growth factor-1 is produced by the liver in response to stimulation by growth hormone. It functions as a mitogen and as an inhibitor of apoptosis.

(Choice C) Somatostatin is produced by cells in the stomach, small bowel and pancreas and inhibits the production and release of most other gastrointestinal hormones, including insulin.

(Choice D) Secretin is a hormone produced in the duodenum in response to increased luminal acidity. It stimulates the release of bicarbonate-rich secretions from the pancreas, gallbladder and duodenum. It also increases the activity of cholecystokinin

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(Choice D) Secretin is a hormone produced in the duodenum in response to increased luminal acidity. It stimulates the release of bicarbonate-rich secretions from the pancreas, gallbladder and duodenum. It also increases the activity of cholecystokinin.

(Choice E) Cholecystokinin is produced by the duodenum in response to a fat or protein-rich meal. It has many functions including inhibition of further gastric emptying, stimulation of pancreatic enzyme secretion and stimulation of bile production and gallbladder contraction.

Educational objective:
Incretin functions by stimulating insulin release following oral consumption of glucose. Incretin-stimulated insulin release is independent of the increase in insulin secretion brought on by elevations in the blood glucose level.

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A 41-year-old man comes to the office due to a 4-month history of fatigue, headache, weight loss, sweating, and palpitations. He is otherwise healthy and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals lid lag and a fine hand tremor. Neck examination reveals mild, diffuse enlargement of the thyroid gland. Laboratory results are as follows:

TSH	10 µU/mL
Free thyroxine (T4)	3.0 ng/mL (normal: 0.9-1.7)
Total triiodothyronine (T3)	400 ng/mL

Which of the following is the most likely cause of this patient's disorder?

A. Elevated thyroxine-binding globulin
B. Graves disease
C. Painless thyroiditis
D. Pituitary tumor
E. Thyroid cancer

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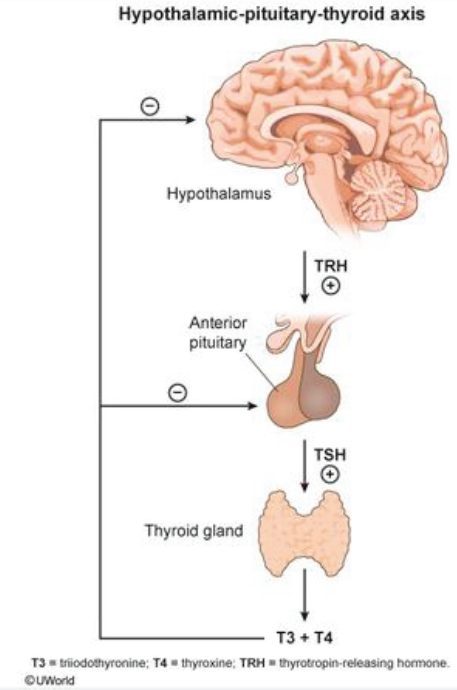
A. Elevated thyroxine-binding globulin (4%)
B. Graves disease (24%)
C. Painless thyroiditis (3%)
D. Pituitary tumor (64%)
E. Thyroid cancer (3%)

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Explanation

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The hypothalamus-pituitary-thyroid axis functions as follows:

- Thyroid hormone is released primarily as thyroxine (T4), with deiodination to triiodothyronine (T3) (the more active form) in peripheral tissues.
- Synthesis of thyroid hormone is driven by TSH secretion from the pituitary.
- TSH is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus.
- Secretion of both TRH and TSH is subject to negative feedback by T3.

Hyperthyroidism typically presents with fatigue, weight loss, and palpitations associated with elevated thyroid hormone levels. Hyperadrenergic signs (eg, lid lag, tremor) are also common. Most patients have primary hyperthyroidism (ie, intrinsic thyroid disorder with increased thyroid hormone release); TSH is low due to feedback suppression.

However, this patient has an **elevated TSH**, suggesting a pituitary etiology (ie, **secondary hyperthyroidism**). The most common cause of secondary hyperthyroidism is a TSH-secreting **pituitary adenoma**. The excess TSH causes generalized hypertrophy of the thyroid gland, manifesting as a **diffuse goiter**.

(Choice A) Most thyroid hormone is transported bound to plasma proteins, primarily thyroxine-binding

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hyperthyroidism). The most common cause of secondary hyperthyroidism is a TSH-secreting **pituitary adenoma**. The excess TSH causes generalized hypertrophy of the thyroid gland, manifesting as a **diffuse goiter**.

(Choice A) Most thyroid hormone is transported bound to plasma proteins, primarily thyroxine-binding globulin (TBG). Estrogen (eg, pregnancy, oral contraceptives) causes increased production of TBG, which lowers free thyroid hormone levels. A brief rise in TSH subsequently increases production of thyroid hormone to saturate the increased TBG binding sites, and the patient returns to a euthyroid state. Total T3 and T4 are elevated, but TSH and free hormone levels are normal.

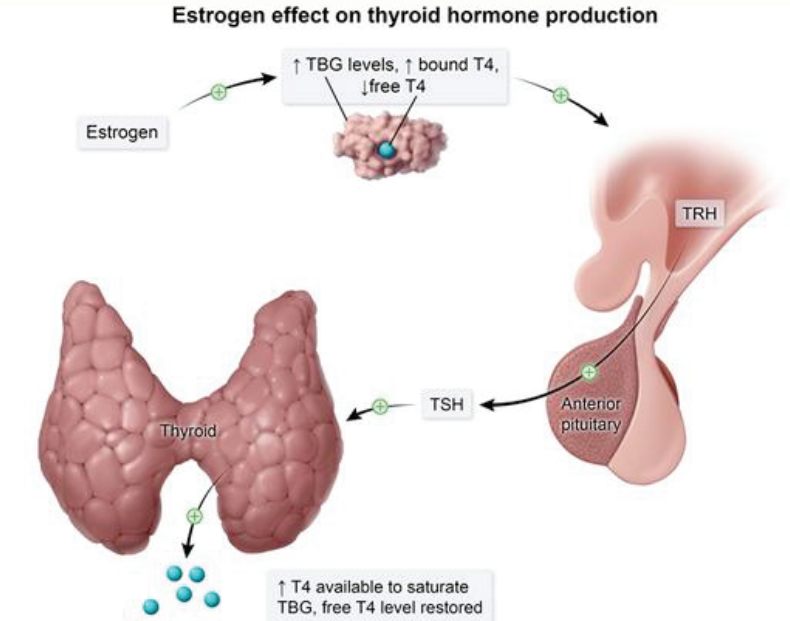
(Choices B and C) Graves disease is caused by autoantibodies that activate the TSH receptor and induce thyroid hormone production. Painless thyroiditis is characterized by autoimmune destruction of thyroid follicles with release of preformed thyroid hormone. Both conditions cause hyperthyroidism with elevated thyroid hormone levels, but TSH is suppressed by feedback inhibition.

(Choice E) Thyroid cancer typically presents with a hard, asymmetric goiter. Adjacent thyroid tissue may be compressed and nonfunctional, but the contralateral lobe can usually compensate and patients are typically euthyroid. Thyroid follicular tumors may occasionally cause hyperthyroidism due to autonomous thyroid hormone production, but TSH is suppressed.

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Educational objective:
The most common cause of secondary hyperthyroidism is a TSH-secreting pituitary adenoma. In addition to hyperthyroid symptoms, TSH causes generalized hypertrophy of the thyroid gland (diffuse goiter). Laboratory evaluation shows elevated levels of thyroid hormone (triiodothyronine and thyroxine) and TSH.

Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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A 25-year-old woman is brought to the emergency department due to progressive lethargy. For the last 3 weeks, she has also had loss of appetite, constipation, muscle weakness, and increased thirst and urination. The patient's medical history is unremarkable. She takes no prescription medications but has been taking large doses of vitamin D supplements in the belief that they are beneficial for her health. The patient does not use tobacco, alcohol, or illicit drugs. On physical examination, she is stuporous and has dry mucous membranes. The metabolic abnormality most likely responsible for this patient's clinical findings can also occur in which of the following conditions?

A. Biliary obstruction
B. Carcinoid syndrome
C. Hemochromatosis
D. Pheochromocytoma
E. Sarcoidosis
F. Wilson disease

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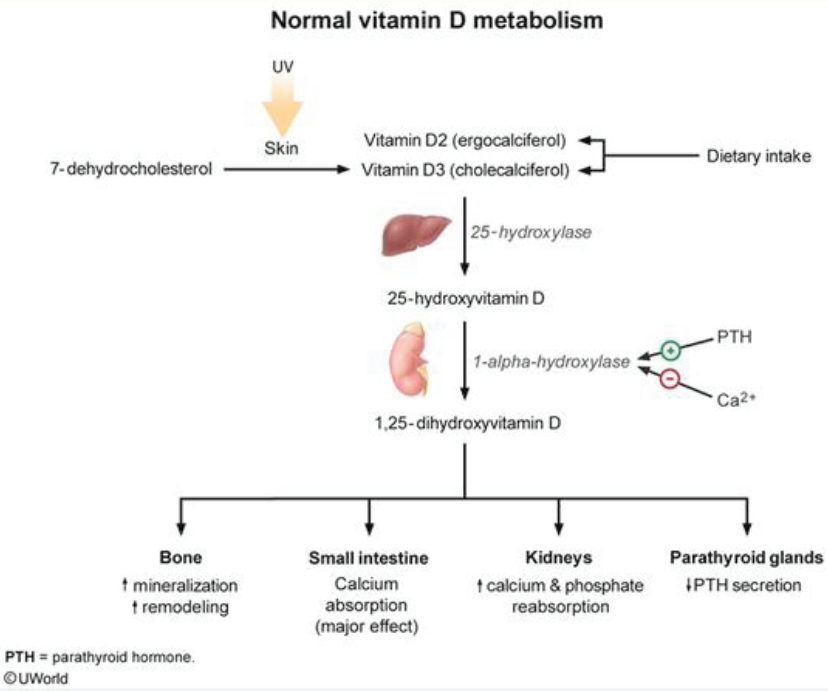
A. Biliary obstruction (5%)
B. Carcinoid syndrome (12%)
C. Hemochromatosis (9%)
D. Pheochromocytoma (6%)
E. Sarcoidosis (60%)
F. Wilson disease (4%)

Correct
60%
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Moderate doses of vitamin D are often recommended for patients with inadequate dietary intake to improve bone mineralization. However, excessive vitamin D can cause symptomatic **hypercalcemia**, with impaired depolarization of neuromuscular membranes (eg, muscle **weakness**, **constipation**, **confusion**) and impaired concentration of urine in the distal tubule (**polyuria/polydipsia**). Chronic vitamin D intoxication can also lead to **renal stone formation** and bone demineralization with associated **bone pain** (although normal vitamin D levels facilitate bone mineralization, toxicity increases osteoclast activity and bone turnover).

Normally, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (the active form) by **1-α-hydroxylase** in the kidneys, a process regulated by parathyroid hormone (PTH). However, patients with **granulomatous diseases** (eg, sarcoidosis, tuberculosis) can have **PTH-independent conversion** due to expression of 1-α-hydroxylase in **activated macrophages**. A similar process can occur in Hodgkin disease and some non-Hodgkin lymphomas.

(Choice A) Biliary obstruction is associated with altered lipid absorption and deficiencies of fat-soluble vitamins (eg, A, D, E, and K).

(Choice B) Carcinoid tumor cells synthesize excessive amounts of serotonin. When these cells metastasize to the liver, the release of serotonin into the systemic circulation results in carcinoid syndrome

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(eg, episodic cutaneous flushing, bronchospasm/wheezing, diarrhea).

(Choice C) Hemochromatosis is associated with excessive intestinal absorption of iron and accumulation in parenchymal organs. Patients classically develop liver cirrhosis, heart failure, skin hyperpigmentation, and diabetes mellitus ("bronze diabetes").

(Choice D) Pheochromocytoma is associated with elevated levels of metanephrines and catecholamines. Patients typically have paroxysmal headache, diaphoresis, tachycardia, and hypertension.

(Choice F) Wilson disease (hepatolenticular degeneration) is characterized by impaired incorporation of copper into ceruloplasmin and defective excretion of excess copper into bile. This leads to elevated blood free copper levels and deposition in the liver (cirrhosis) and brain (motor abnormalities, psychiatric symptoms).

Educational objective:
Excessive vitamin D intake can lead to hypercalcemia and cause mental status changes, muscle weakness, constipation, and polyuria/polydipsia. Activated macrophages in sarcoidosis and other granulomatous diseases express 1-α-hydroxylase, leading to excess production of 1,25-dihydroxyvitamin D and hypercalcemia.

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A 65-year-old woman comes to the clinic for follow up of type 2 diabetes mellitus. Medical history is notable for hypertension, stable coronary artery disease, and heart failure with preserved ejection fraction. Blood pressure is 144/95 mm Hg. Physical examination shows no murmurs, and the lungs are clear on auscultation. Fasting glucose is 122 mg/dL and hemoglobin A1c is 7.8%. The remainder of the laboratory results, including hepatic and renal markers, are normal. The patient is given a prescription for canagliflozin. She should be counseled on which of the following potential complications prior to initiation of this medication?

A. Fluid overload
B. Hypoglycemia
C. Lactic acidosis
D. Urinary infection
E. Weight gain

Submit

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A 65-year-old woman comes to the clinic for follow up of type 2 diabetes mellitus. Medical history is notable for hypertension, stable coronary artery disease, and heart failure with preserved ejection fraction. Blood pressure is 144/95 mm Hg. Physical examination shows no murmurs, and the lungs are clear on auscultation. Fasting glucose is 122 mg/dL and hemoglobin A1c is 7.8%. The remainder of the laboratory results, including hepatic and renal markers, are normal. The patient is given a prescription for canagliflozin. She should be counseled on which of the following potential complications prior to initiation of this medication?

A. Fluid overload (1%)
B. Hypoglycemia (4%)
C. Lactic acidosis (0%)
D. Urinary infection (90%)
E. Weight gain (2%)

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Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss

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• Pioglitazone	resistance	failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** =

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PPAR-γ = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.

Sodium-glucose cotransporter 2 (SGLT2) is a high-capacity transport protein that reabsorbs 90% of filtered glucose in the proximal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. The decreased reabsorption of sodium and glucose also induces **osmotic diuresis**, leading to a decrease in blood pressure and a lower rate of hospitalization for heart failure.

However, the glycosuria induced by SGLT2 inhibitors creates a more favorable environment for pathogenic bacteria and fungi in the genitourinary tract and perineum. This leads to an increased risk for **urinary tract infections** (eg, pyelonephritis), **genital mycotic infections** (eg, vaginitis), and **necrotizing fasciitis** of the perineum (Fournier gangrene). Other adverse effects include hypovolemia, which can lead to orthostatic hypotension and acute kidney injury.

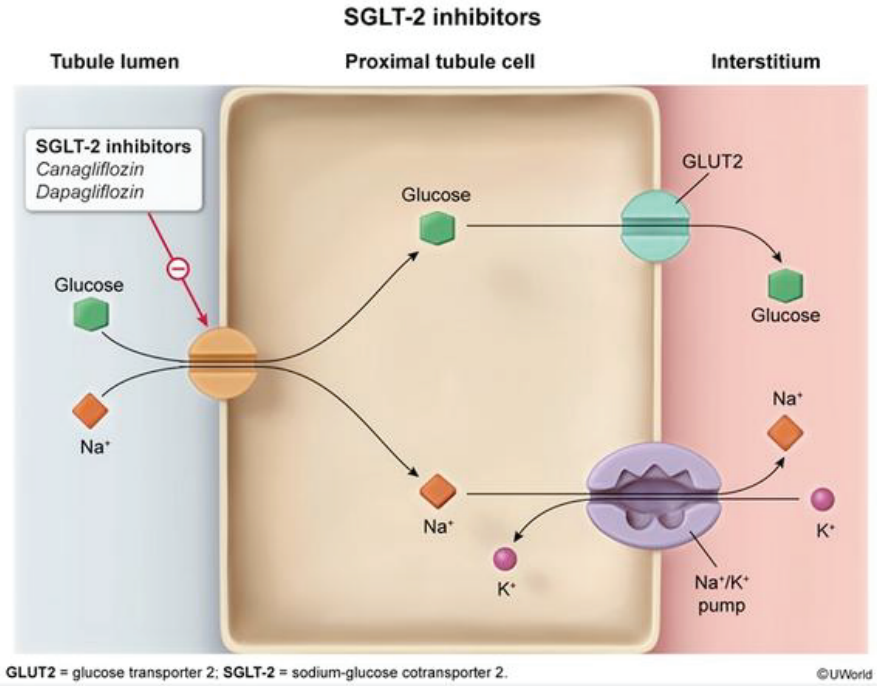
(Choice A) Thiazolidinediones (eg, pioglitazone) increase the reabsorption of sodium in the renal collecting tubule; this can lead to significant fluid retention, particularly in patients with heart failure. In contrast, SGLT2 inhibitors reduce fluid retention.

(Choices B and E) Exogenous insulin and sulfonylureas, which stimulate endogenous insulin secretion,

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PPAR-γ = peroxisome proliferator–activated receptor γ; **SGLT2** = sodium-glucose cotransporter 2.

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GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

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contrast, SGLT2 inhibitors reduce fluid retention.

(Choices B and E) Exogenous insulin and sulfonylureas, which stimulate endogenous insulin secretion, can cause hypoglycemia and weight gain. SGLT2 inhibitors carry a low risk of hypoglycemia because the glucose-lowering effect is proportionate to the filtered glucose load; also, renal glucose wasting typically induces mild weight loss.

(Choice C) Metformin inhibits hepatic gluconeogenesis, leading to the accumulation of lactate. Patients with decreased lactate clearance (eg, renal or hepatic dysfunction, congestive heart failure) can have excessive accumulation of lactate, leading to lactic acidosis.

Educational objective:

Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. However, the resulting glycosuria can lead to genitourinary tract infections and necrotizing fasciitis of the perineum.

References

- Risks associated with SGLT2 inhibitors: an overview.

Pharmacology Endocrine, Diabetes & Metabolism Antidiabetic drugs

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A 28-year-old woman comes to the office due to progressively worsening eye irritation and double vision over the last 2 months. She also reports unintentional weight loss, mood swings, and palpitations. The patient has no prior medical problems and takes no medications. She has no known drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/70 mm Hg, and pulse is 110/min and regular. Physical examination shows bilateral conjunctival redness and severe proptosis. Appropriate therapy is begun. On a follow-up visit 4 weeks later, her eye symptoms have improved, and examination reveals a small decrease in proptosis with no redness. The drug that improved her ocular symptoms most likely did so by affecting which of the following?

A. Inflammatory infiltration
B. Iodine organification
C. Iodine uptake by the thyroid
D. Sympathetic hyperactivity
E. T3/T4 release by the thyroid

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- ✓ A. Inflammatory infiltration (48%)
- B. Iodine organification (29%)
- C. Iodine uptake by the thyroid (3%)
- D. Sympathetic hyperactivity (8%)
- E. T3/T4 release by the thyroid (9%)

Correct

48%

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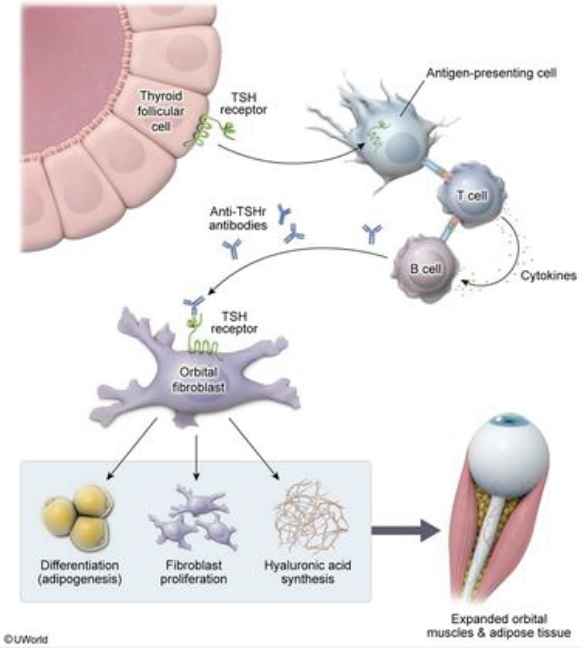
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Pathogenesis of Graves ophthalmopathy



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This patient has **Graves disease** with hyperthyroidism (weight loss, palpitations, tachycardia) and significant ophthalmopathy (proptosis, diplopia). Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies**, which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor is present on fibroblasts, adipocytes, and other cell types. **Graves ophthalmopathy** is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies, which leads to excess deposition of extracellular glycosaminoglycans; this is accompanied by T-cell activation and **inflammatory infiltration**. The resultant expansion of extraocular muscles and retro-orbital tissues with the orbit displaces the globe forward, and dysfunction of the extraocular muscles causes restricted extraocular movements and diplopia.

Glucocorticoids (eg, prednisone) decrease peripheral conversion of T4 to T3, but it is their **anti-inflammatory** effects that improve Graves ophthalmopathy. Glucocorticoids decrease the severity of inflammation and reduce the excess extraocular volume. They also can prevent worsening of ophthalmopathy induced by radioactive iodine treatment.

(Choices B, C, and E) Antithyroid drugs (eg, methimazole, propylthiouracil) inhibit thyroid peroxidase, leading to decreased iodine organification and coupling of iodotyrosines. Certain oxoanions (eg, perchlorate, pertechnetate) inhibit the sodium-iodide symporter and reduce iodine uptake by the thyroid. These agents ultimately lead to reduced production and release of thyroid hormone but do not alter the

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ophthalmopathy induced by radioactive iodine treatment.

(Choices B, C, and E) Antithyroid drugs (eg, methimazole, propylthiouracil) inhibit thyroid peroxidase, leading to decreased iodine organification and coupling of iodotyrosines. Certain oxoanions (eg, perchlorate, pertechnetate) inhibit the sodium-iodide symporter and reduce iodine uptake by the thyroid. These agents ultimately lead to reduced production and release of thyroid hormone but do not alter the inflammatory process in Graves ophthalmopathy.

(Choice D) Sympathetic activation secondary to hyperthyroidism is responsible for a number of symptoms, including palpitations and tremors. Beta blockers can provide rapid symptomatic relief while awaiting definitive therapy. Although lid lag (which is seen in hyperthyroidism of any cause) would improve with beta blockers, the specific features of Graves ophthalmopathy (eg, diplopia, proptosis) would not be affected.

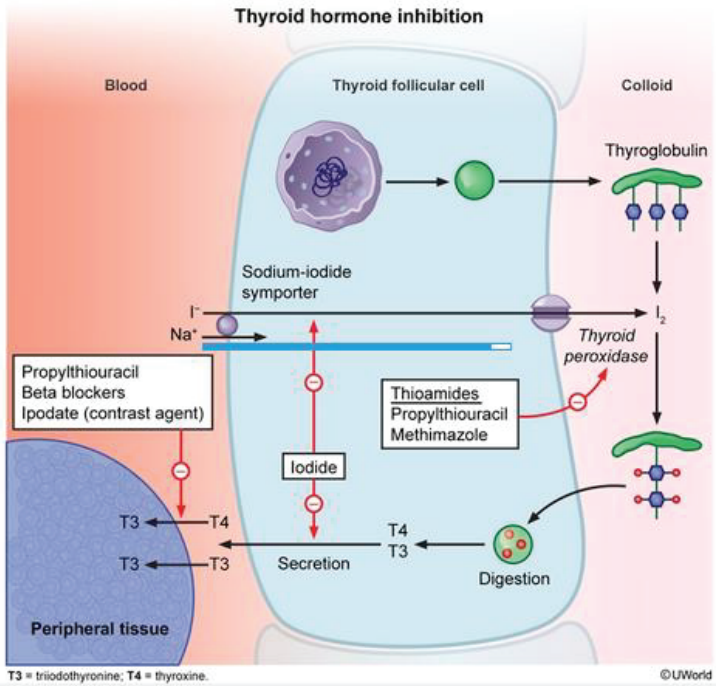
Educational objective:
Graves ophthalmopathy is caused by stimulation of orbital fibroblasts by thyrotropin receptor antibodies and cytokines released by activated T-cells. Excess deposition of extracellular glycosaminoglycans and inflammatory infiltration lead to expansion of extraocular muscles and retro-orbital tissues. Glucocorticoids improve Graves ophthalmopathy by decreasing the severity of inflammation and reducing the excess extraocular volume.

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ophthalmopathy induced by radioactive iodine treatment

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A 43-year-old woman comes to the office to discuss amenorrhea. She began having irregular menses 2 years ago, and her last menstrual period was 9 months ago. Family history is unremarkable. Laboratory studies show an increased serum prolactin level, a normal TSH level, and an undetectable β-hCG concentration. Serum calcium is normal. MRI reveals a 6-mm pituitary adenoma. The patient refuses medical and surgical therapy as she is happy about not having menstrual periods. If left untreated, this patient is at greatest risk of developing which of the following?

A. Cortical stroke
B. Gastric ulcer
C. Loss of bone mass
D. Myocardial infarction
E. Secondary diabetes mellitus

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A. ~~Cortical stroke~~ (12%)
B. ~~Gastric ulcer~~ (2%)
✓ C. Loss of bone mass (75%)
D. Myocardial infarction (2%)
E. ~~Secondary diabetes mellitus~~ (7%)

Correct

75%
Answered correctly

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Prolactinoma	
Clinical features	• **Premenopausal women**: Oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass-effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms

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Treatment	• Trans-sphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms (eg, hypopituitarism, headache, bitemporal hemianopsia) due to pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas

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this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common and may lead to recurrent peptic ulcers (Zollinger-Ellison syndrome). However, almost all patients with MEN type 1 have hyperparathyroidism with hypercalcemia.

(Choice D) Early menopause (age <40) is associated with an increased risk of cardiovascular events, but the effect of the prolactinoma-induced low estrogenic state on cardiovascular risk in older women is unclear.

(Choice E) Excess growth hormone secretion from a somatotroph pituitary adenoma can lead to diabetes mellitus due to increased insulin resistance in peripheral tissues. However, adults typically present with acromegaly.

Educational objective:
Hyperprolactinemia suppresses secretion of GnRH, which leads to reduced estrogen in women. Low estrogen levels are a risk factor for accelerated bone loss.

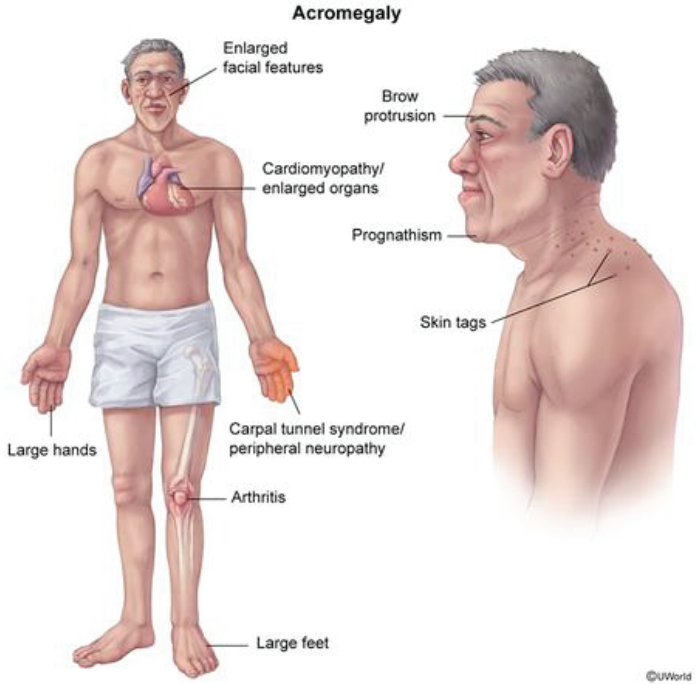
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A 56-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She is managing her condition with a healthy diet and regular exercise and is on the maximum tolerated dose of metformin. Despite this, the patient's diabetes has been inadequately controlled for the last 6 months, with an average fasting glucose level of 170 mg/dL and a hemoglobin A1c of 8.0%. She has no known diabetes-related complications. Medical history includes hypertension, for which she takes lisinopril and amlodipine. After discussing various medication options, it is decided to add pioglitazone to her current regime. Before starting this medication, this patient should be educated about which of the following adverse drug effects?

A. Agranulocytosis
B. Hepatic injury
C. Hypoglycemia
D. Lactic acidosis
E. Orthostatic hypotension
F. Weight gain and edema

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condition with a healthy diet and regular exercise and is on the maximum tolerated dose of metformin. Despite this, the patient's diabetes has been inadequately controlled for the last 6 months, with an average fasting glucose level of 170 mg/dL and a hemoglobin A1c of 8.0%. She has no known diabetes-related complications. Medical history includes hypertension, for which she takes lisinopril and amlodipine. After discussing various medication options, it is decided to add pioglitazone to her current regime. Before starting this medication, this patient should be educated about which of the following adverse drug effects?

A. ~~Agranulocytosis~~ (2%)
B. ~~Hepatic injury~~ (5%)
C. ~~Hypoglycemia~~ (12%)
D. ~~Lactic acidosis~~ (2%)
E. Orthostatic hypotension (2%)
✓ F. Weight gain and edema (75%)

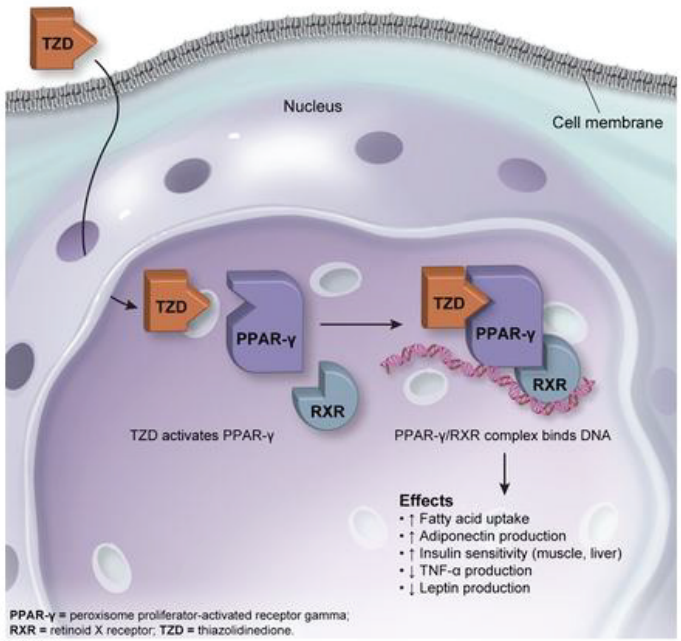
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Thiazolidinedione mechanism of action



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Thiazolidinediones (TZDs) (eg, pioglitazone) activate peroxisome proliferator-activated receptor gamma, a transcriptional regulator that affects expression of genes involved in glucose and lipid metabolism. TZDs cause reduced insulin resistance and a decrease in blood glucose levels. Because their effect requires an alteration in gene transcription and protein synthesis, maximal glucose lowering may take place days to weeks after initiating therapy.

The main side effect of TZDs is **fluid retention** due to increased sodium reabsorption in the renal collecting tubules and increased vascular permeability in adipose tissue. This can cause water weight gain, peripheral edema, and decompensation of underlying **congestive heart failure**. Fluid retention is often worse when TZDs are given with insulin. TZDs also cause **adipose weight gain**, likely due to increased fat storage in adipocytes and an increased number of adipocytes in subcutaneous tissue.

(Choice A) Agranulocytosis is seen with certain antithyroid medications (eg, methimazole) and is a rare complication of sulfonylurea therapy. It is not seen with TZDs.

(Choice B) Hepatic toxicity was seen with an older TZD, troglitazone, which is no longer available. The current TZDs (pioglitazone and rosiglitazone) do not cause significant hepatotoxicity.

(Choice C) TZDs increase insulin sensitivity rather than insulin secretion. As a result, they have a low risk

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complication of sulfonylurea therapy. It is not seen with TZDs.

(Choice B) Hepatic toxicity was seen with an older TZD, troglitazone, which is no longer available. The current TZDs (pioglitazone and rosiglitazone) do not cause significant hepatotoxicity.

(Choice C) TZDs increase insulin sensitivity rather than insulin secretion. As a result, they have a low risk of hypoglycemia, although they can increase the risk if used in combination with insulin or sulfonylureas.

(Choice D) Lactic acidosis is a potential side effect of metformin, although it is rare when used in patients with normal renal, hepatic, and cardiac function.

(Choice E) Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin) can induce osmotic diuresis, leading to volume depletion and orthostatic hypotension. TZDs do not commonly cause orthostatic hypotension.

Educational objective:
Thiazolidinediones (eg, pioglitazone) can cause fluid retention, leading to peripheral edema and weight gain. The excess fluid can potentially exacerbate underlying congestive heart failure.

References

- Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a

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A 32-year-old previously healthy woman comes to the office due to several weeks of anxiety, palpitations, excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

A. Anxiety
B. Diaphoresis
C. Exophthalmos
D. Hand tremor
E. Heat intolerance
F. Palpitations

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excessive sweating, and thinning hair. The symptoms have progressively worsened and interfered significantly with her daily activities. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/70 mm Hg and pulse is 104/min. On physical examination, there is lid lag, moderate exophthalmos, and fine tremors of the outstretched hands. After the diagnosis is made, she is prescribed propranolol for immediate symptom control. Which of the following findings is most likely to persist in this patient despite this therapy?

A. Anxiety (3%)
B. Diaphoresis (6%)
C. Exophthalmos (84%)
D. Hand tremor (2%)
E. Heat intolerance (2%)
F. Palpitations (0%)

Correct

84%
Answered correctly

40 secs
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General manifestations of hyperthyroidism	
Symptoms	• Anxiety & insomnia • Palpitations • Heat intolerance • Increased perspiration • Weight loss without decreased appetite
Physical examination	• Goiter • Hypertension • Tremors involving fingers/hands • Hyperreflexia • Proximal muscle weakness • Lid lag • Atrial fibrillation

Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the

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- Atrial fibrillation

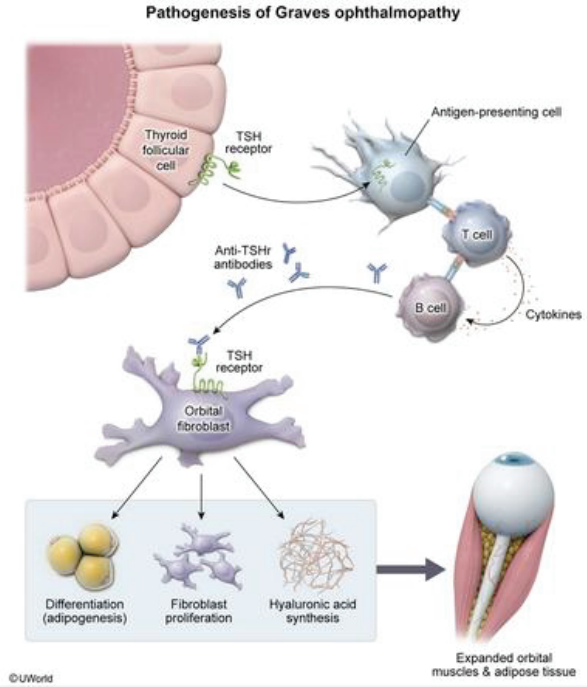
Graves disease is an autoimmune disorder characterized by autoantibodies that bind to and activate the TSH receptor (**thyrotropin receptor antibodies** [TRAb]). In the thyroid, TRAb triggers release of thyroid hormones, leading to thyrotoxicosis. Hyperthyroidism causes increased expression of **beta-adrenergic receptors** in various organs, and the subsequent hyperadrenergic state can result in hypertension, tremor, heat intolerance, palpitations/tachycardia, and hyperreflexia **(Choices D, E, and F)**. Patients with Graves disease are frequently given beta-adrenergic blocking medications (eg, propranolol) to control these manifestations while awaiting definitive management.

TSH receptors are also present on fibroblasts, adipocytes, and other tissues. Graves ophthalmopathy results from stimulation of orbital fibroblasts and adipocytes by TRAb and activated T cells. The fibroblasts secrete excess amounts of glycosaminoglycans, leading to expansion of the ground substance of retro-orbital tissues. This, along with excess adipose deposition, displaces the globe forward (**exophthalmos**) and leads to restricted movement of the extraocular muscles (eg, diplopia). These manifestations are not mediated by thyroid hormone or adrenergic stimulation and do not respond to beta blockers. However, as they are **immune mediated**, the manifestations of Graves ophthalmopathy usually respond to **glucocorticoid therapy**.

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mediated by thyroid hormone or adrenergic stimulation and do not respond to beta blockers. However, as they are **immune mediated**, the manifestations of Graves ophthalmopathy usually respond to **glucocorticoid therapy**.

(Choice A) Although beta blockers can cause fatigue and depressive symptoms, they help reduce fatigue and mood lability in patients with Graves disease by ameliorating sympathetic overactivation. Beta blockers can also help blunt the physical manifestations of anxiety.

(Choice B) Apocrine sweat glands are stimulated primarily by catecholamines; beta blockers can reduce secretory activity. By contrast, eccrine sweat glands are directly innervated by cholinergic fibers. However, centrally acting beta blockers (eg, propranolol) can modulate eccrine activity and reduce emotionally driven (eg, anxiety) stimulation of eccrine sweating.

Educational objective:
Hyperthyroidism causes a hyperadrenergic state characterized by hypertension, palpitations/tachycardia, sweating, heat intolerance, tremor, and hyperreflexia. Beta blockers can relieve these symptoms. Exophthalmos in Graves disease is due to an immune-mediated increase in orbital soft tissue mass and does not improve with beta blockers.

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A 25-year-old woman comes to the office due to a 2-week history of neck pain. The patient had an upper respiratory infection a month ago, during which she experienced nasal congestion, rhinorrhea, and a cough productive of clear sputum; her respiratory symptoms lasted for 5 days and resolved spontaneously. The patient then felt well until 2 weeks ago, when she developed pain in the anterior neck associated with mild fever, palpitations, and excessive sweating. She is otherwise healthy and takes no medications. Pulse is 110/min. The thyroid gland is tender to palpation and diffusely enlarged. Other findings include sweaty palms, fine hand tremor, and brisk deep tendon reflexes. Laboratory studies show suppressed TSH and elevated free thyroxine levels. Erythrocyte sedimentation rate is 70 mm/hr. Which of the following additional findings is most likely to be present in this patient at this time?

A. Elevated thyroid peroxidase antibody level
B. Low radioactive iodine uptake
C. Low serum thyroglobulin
D. Low serum triiodothyronine level

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A. Elevated thyroid peroxidase antibody level (27%)
B. Low radioactive iodine uptake (42%)
C. Low serum thyroglobulin (25%)
D. Low serum triiodothyronine level (5%)

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Explanation

Subacute thyroiditis	
Pathogenesis	• Postviral inflammatory response • Destruction of thyroid follicles with release of preformed thyroid hormone
Clinical features	• Painful/tender goiter • Fever • Initial hyperthyroid phase → hypothyroid phase → return to euthyroid
Diagnostic testing	• Elevated thyroid hormone, suppressed TSH (hyperthyroid phase) • Elevated serum thyroglobulin • Elevated erythrocyte sedimentation rate • Low radioiodine uptake

This patient has **primary hyperthyroidism** (ie, intrinsic thyroid disease), confirmed with elevated free thyroxine and low TSH. Common nonspecific findings in hyperthyroidism include diaphoresis, tachypalpitations, tremor, brisk reflexes, and lid lag. In addition, she has features suggesting **subacute (granulomatous, de Quervain) thyroiditis** (ST), including fever; a painful, tender goiter; and an elevated

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	• Low radioiodine uptake

This patient has **primary hyperthyroidism** (ie, intrinsic thyroid disease), confirmed with elevated free thyroxine and low TSH. Common nonspecific findings in hyperthyroidism include diaphoresis, tachypalpitations, tremor, brisk reflexes, and lid lag. In addition, she has features suggesting **subacute (granulomatous, de Quervain) thyroiditis** (ST), including fever; a painful, tender goiter; and an elevated erythrocyte sedimentation rate (nonspecific marker for inflammation).

ST characteristically follows a **viral infection** and is thought to be due to a cross-reacting inflammatory response with activation of cytotoxic T lymphocytes. Diagnostic findings in ST include:

- elevated thyroid hormone levels (ie, thyroxine [T4], triiodothyronine [T3]) due to the destruction of thyroid follicles and **release of preformed thyroid hormone**.
- **elevated thyroglobulin**, which is released from thyroid follicles with thyroid hormone.
- suppressed TSH due to feedback inhibition by thyroid hormone on the pituitary.
- **low radioactive iodine uptake** (ie, radioiodine thyroid scintigraphy) reflecting decreased thyroid metabolic activity and organification of iodine due to loss of TSH stimulation.
- diffuse enlargement of the gland with **decreased blood flow** on thyroid ultrasound.

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• Low radioiodine uptake

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Differential diagnosis of thyroiditis

Painful thyroiditis	Painless thyroiditis	Graves	Fibrotic
Pain & tenderness Systemic symptoms	Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	+TSI/TRAb ↑ Thyroid hormone synthesis	Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin;
TRAb = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

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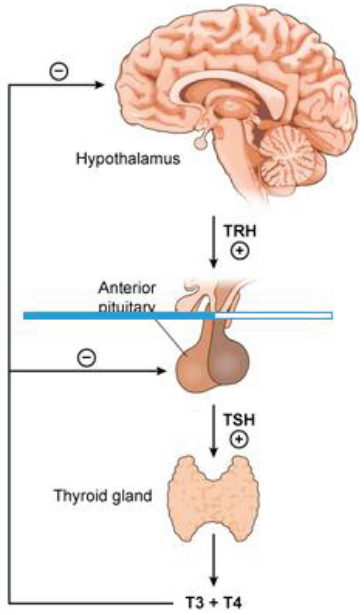
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• Low radioiodine uptake

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Hypothalamic-pituitary-thyroid axis



T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin-releasing hormone.

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metabolic activity and organification of iodine due to loss of TSH stimulation.

- diffuse enlargement of the gland with **decreased blood flow** on thyroid ultrasound.

Following the hyperthyroid phase, patients experience transient hypothyroidism due to depletion of thyroid colloid and then slowly return to a euthyroid state.

(Choice A) Thyroid peroxidase antibodies are a marker for autoimmune thyroid disorders, including postpartum and chronic lymphocytic (Hashimoto) thyroiditis and Graves disease. Goiter is common in these conditions but is painless and nontender.

(Choice C) Exogenous thyroid hormone intake (eg, levothyroxine, porcine thyroid extract) can cause hyperthyroidism with suppression of TSH and decreased endogenous release of thyroid hormone and thyroglobulin. However, the native thyroid is not enlarged and is often atrophic.

(Choice D) Euthyroid sick syndrome (low T3 syndrome) is a characteristic set of thyroid function abnormalities in patients with severe systemic illness. It resembles mild, central hypothyroidism with normal/low TSH and low T3 levels. The thyroid is not enlarged or tender, and the syndrome is not usually seen following ordinary upper respiratory illnesses.

Educational objective:

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postpartum and chronic lymphocytic (Hashimoto) thyroiditis and Graves disease. Goiter is common in these conditions but is painless and nontender.

(Choice C) Exogenous thyroid hormone intake (eg, levothyroxine, porcine thyroid extract) can cause hyperthyroidism with suppression of TSH and decreased endogenous release of thyroid hormone and thyroglobulin. However, the native thyroid is not enlarged and is often atrophic.

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Educational objective:
Subacute (granulomatous, de Quervain) thyroiditis presents with fever; a painful, tender goiter; and an elevated erythrocyte sedimentation rate. Patients initially develop hyperthyroidism due to the destruction of thyroid follicles and release of preformed thyroid hormone. TSH is suppressed due to feedback inhibition on the pituitary; as a result, thyroid metabolic activity and organification of iodine are decreased, and radioactive iodine uptake is low.

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A 22-year-old woman comes to the emergency department due to fever and a sore throat. Her medical history is significant for Graves disease, for which she recently began taking an antithyroid medication. The patient has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. She works as a teacher at an elementary school. Temperature is 38.9 C (102 F), blood pressure is 110/70 mm Hg, and pulse is 90/min. Physical examination shows an erythematous pharynx and a normal-sized thyroid. There is no tremor of the outstretched hands. Which of the following is the most likely cause of this patient's current condition?

A. Acute adrenal insufficiency
B. Drug-induced granulocyte destruction
C. Excessive thyroid suppression
D. Thyroid hormone–induced severe hypermetabolism
E. Viral destruction of neutrophils

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A 22-year-old woman comes to the emergency department due to fever and a sore throat. Her medical history is significant for Graves disease, for which she recently began taking an antithyroid medication. The patient has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. She works as a teacher at an elementary school. Temperature is 38.9 C (102 F), blood pressure is 110/70 mm Hg, and pulse is 90/min. Physical examination shows an erythematous pharynx and a normal-sized thyroid. There is no tremor of the outstretched hands. Which of the following is the most likely cause of this patient's current condition?

A. Acute adrenal insufficiency (1%)
B. Drug-induced granulocyte destruction (68%)
C. Excessive thyroid suppression (5%)
D. Thyroid hormone–induced severe hypermetabolism (3%)
E. Viral destruction of neutrophils (20%)

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Complications of Graves disease treatment	
Treatment	**Adverse effects**
Antithyroid drugs (thionamides)	• **Agranulocytosis** • Methimazole: 1st-trimester teratogen • Propylthiouracil: **Hepatic failure**
Radioiodine ablation	• Permanent hypothyroidism • Worsening of ophthalmopathy • Possible radiation side effects
Surgery	• Permanent hypothyroidism • Risk of recurrent laryngeal nerve damage • Risk of hypoparathyroidism

Antithyroid drugs (eg, propylthiouracil [PTU], methimazole) inhibit thyroid peroxidase and are used to decrease thyroid hormone production in patients with hyperthyroidism (eg, Graves disease). However, antithyroid drugs are associated with an increased risk for **agranulocytosis**, typically in the first few

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Antithyroid drugs (eg, propylthiouracil [PTU], methimazole) inhibit thyroid peroxidase and are used to decrease thyroid hormone production in patients with hyperthyroidism (eg, Graves disease). However, antithyroid drugs are associated with an increased risk for **agranulocytosis**, typically in the first few months of therapy. This is an idiosyncratic and potentially life-threatening side effect of therapy and is likely due to both immune-mediated effects (via generation of antineutrophil cytoplasmic antibodies) and direct bone marrow toxicity (via generation of reactive oxygen species).

Patients with drug-induced agranulocytosis (absolute neutrophil count <500/mm^3) are at risk for **severe infection**; oropharyngeal infection (eg, fever, **sore throat**, **oral ulcerations**) is the most common initial manifestation, and sepsis can develop quickly thereafter. **Complete blood count with differential** will show **neutropenia** without anemia or thrombocytopenia; bone marrow biopsy will reveal a reduction in granulocyte precursors. Agranulocytosis is reversible on **discontinuation of the drug**.

(Choice A) Patients with autoimmune thyroid disease are at risk for other autoimmune endocrinopathies, including adrenal insufficiency. However, acute adrenal crisis typically presents with refractory hypotension, vomiting, abdominal pain, and weakness.

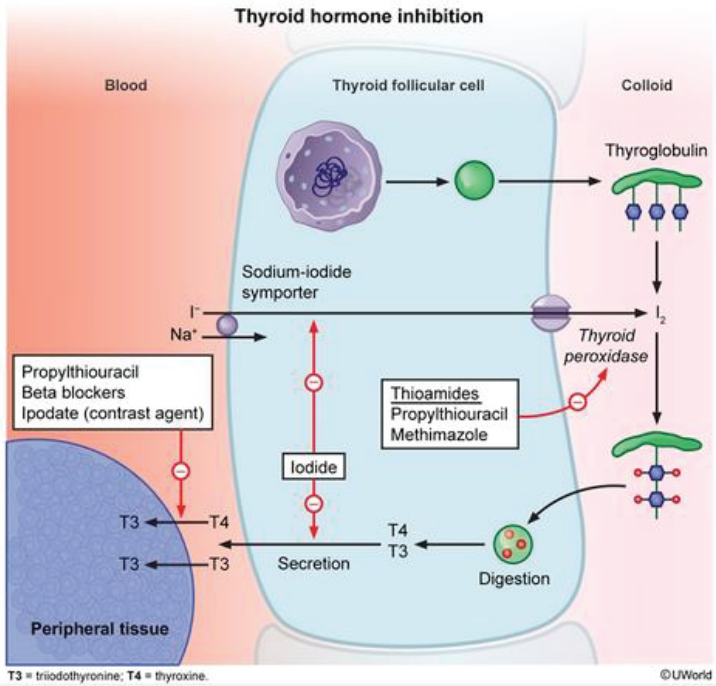
(Choices C and D) Excessive suppression of thyroid function by antithyroid drugs leads to a hypothyroid state characterized by fatigue, weight gain, cold intolerance, and hair and skin changes. Undertreatment

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Antithyroid drugs (eg, propylthiouracil [PTU], methimazole) inhibit thyroid peroxidase and are used to

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including adrenal insufficiency. However, acute adrenal crisis typically presents with refractory hypotension, vomiting, abdominal pain, and weakness.

(Choices C and D) Excessive suppression of thyroid function by antithyroid drugs leads to a hypothyroid state characterized by fatigue, weight gain, cold intolerance, and hair and skin changes. Undertreatment would result in a residual hyperthyroid state, with anxiety, tachycardia, tremor, and heat intolerance. Neither hyper- nor hypothyroidism typically present with a febrile pharyngeal infection.

(Choice E) A number of viruses can cause neutropenia, including HIV, viral hepatitis (A, B, C), and the herpesvirus group (varicella zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus-6). However, the recent initiation of an antithyroid drug makes drug-induced agranulocytosis more likely.

Educational objective:

Agranulocytosis is a serious complication of antithyroid drugs (eg, methimazole, propylthiouracil) that results from drug-induced granulocyte destruction and consequent neutropenia. Initial manifestations often include fever, sore throat, and oral ulcerations. If drug-induced agranulocytosis is suspected, the drug should be discontinued immediately and a complete blood count with differential should be obtained to help confirm the diagnosis.

References

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A 48-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She has had diabetes for 10 years with gradually worsening glycemic control despite taking multiple oral antidiabetic agents. Three months ago, the patient discontinued her oral medications (except for metformin) and started a daily injection of insulin glargine; she has had multiple visits with the diabetes educator since then to review injection technique and titrate up the dose. However, the patient reports a 4.5-kg (10-lb) weight gain since starting insulin. She says, "I feel like I need to eat more. If that's how insulin is going to be, then I don't want to continue it." Which of the following is the most appropriate response to this patient's statement?

A. "Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?"

B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?"

C. "Sometimes stress can increase your appetite. How are things in your life right now?"

D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects."

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for 10 years with gradually worsening glycemic control despite taking multiple oral antidiabetic agents. Three months ago, the patient discontinued her oral medications (except for metformin) and started a daily injection of insulin glargine; she has had multiple visits with the diabetes educator since then to review injection technique and titrate up the dose. However, the patient reports a 4.5-kg (10-lb) weight gain since starting insulin. She says, "I feel like I need to eat more. If that's how insulin is going to be, then I don't want to continue it." Which of the following is the most appropriate response to this patient's statement?

A. ~~"Regular exercise can reduce insulin-induced weight gain. What are your current exercise habits?"~~ (15%)

✓ B. "Some patients eat more after starting insulin because they fear their sugar may drop. Have you noticed that happening to you?" (49%)

C. ~~"Sometimes stress can increase your appetite. How are things in your life right now?"~~ (18%)

D. "Unfortunately, although insulin controls diabetes, it can cause weight gain. But the benefits outweigh the side effects." (16%)

Correct

49%

01 min, 10 secs

11/03/2020

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Insulin-induced weight gain	
Physiologic factors	• Increased peripheral glucose uptake • Increased adipose fatty acid uptake • Reduced renal glucose losses
Behavioral factors	• Less rigorous dietary adherence • Eating/snacking in response to hypoglycemic symptoms
Patient counseling	• Review for changes in diet • Ask about hypoglycemic symptoms

Insulin therapy for diabetes mellitus commonly causes **weight gain** due to increased peripheral glucose uptake, increased adipose lipid deposition, and reduced renal glucose loss (due to normalization of blood glucose, which reduces the filtered glucose load). Behavioral factors, including snacking and less rigorous adherence to dietary recommendations, can also contribute. Weight gain is especially pronounced in patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine).

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patients with type 2 diabetes who typically have high circulating levels of insulin and preexisting obesity.

This patient has experienced weight gain after initiating a long-acting insulin analogue (ie, insulin glargine). Insulin normally suppresses appetite, but this patient reports **increased need to eat**, which suggests that the weight gain may not be simply due to the metabolic effects of insulin. Specifically, this patient may be eating more to suppress **feelings of hypoglycemia**.

To address this patient's insulin-induced weight gain, the clinician should obtain additional history to elicit the **patient's perspective** on appetite, recent changes in **dietary patterns**, and associated **hypoglycemic symptoms**. Once the causes are better understood, several strategies, including dietary modification and changes to the insulin regimen, can mitigate insulin-induced weight gain.

(Choice A) Periodic review of exercise habits is recommended for patients with diabetes. However, this patient has already stated that appetite is her primary concern, so this should be explored first.

(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

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(Choice C) Patients can gain weight due to a variety of factors. In addition to physiologic factors, stress often alters diet and exercise habits, leading to weight gain. However, this patient's weight gain is temporally associated with the initiation and titration of insulin, which makes insulin the most reasonable culprit. If the issue is not resolved after addressing the patient's insulin regimen, other factors can be explored.

(Choice D) Although the benefits of improved glycemic control with insulin generally outweigh the negative effects of weight gain, this statement does not address the patient's concerns and could miss an opportunity to improve the insulin program.

Educational objective:

Insulin can cause weight gain due to physiologic (eg, increased peripheral glucose uptake, reduced renal loss of glucose) and behavioral (eg, increased snacking in response to hypoglycemia, less rigorous attention to diet) factors. Counseling should elicit the patient's perspective on appetite, changes in dietary patterns, and hypoglycemic symptoms.

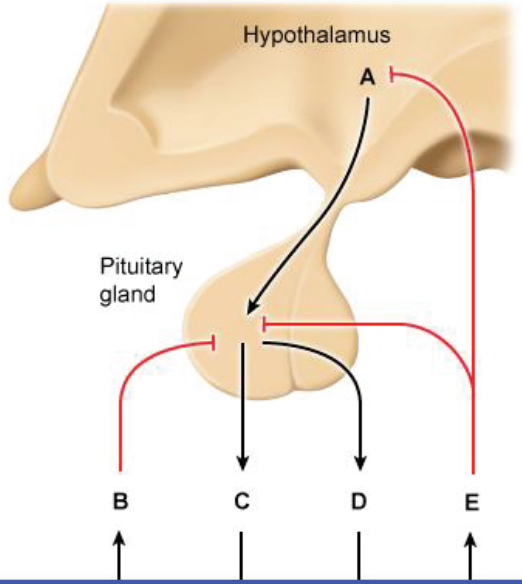
References

- Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done?

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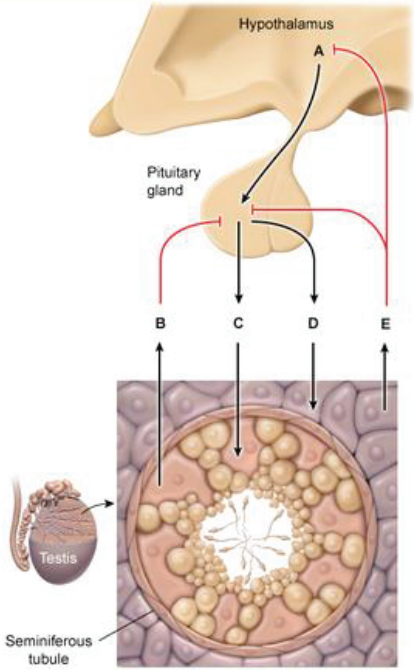
A 14-year-old boy is brought to the physician by his mother. She is concerned because although tall, her son looks much younger than his peers and shows no signs of "masculinity." On physical examination, the boy has poorly developed secondary sexual characteristics. He is unable to distinguish smells but has good visual acuity. Which of the following pathways is most likely defective in this patient?



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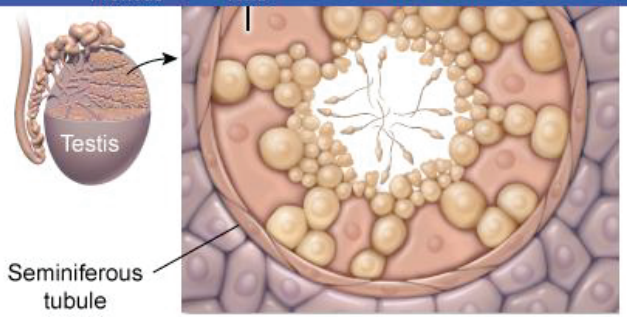
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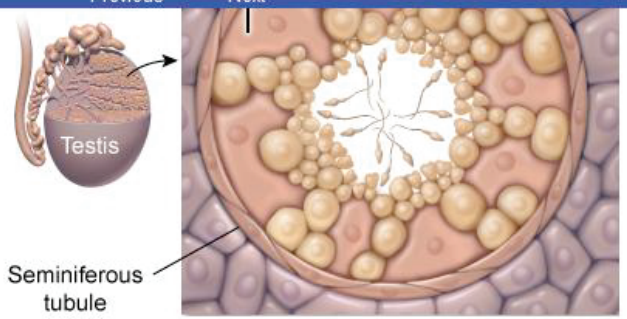


- A.A
- B.B
- C.C
- D.D
- E.E

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- A.A (57%)
- B.B (4%)
- C.C (8%)
- D.D (20%)
- E.E (8%)

Correct

57%

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This patient has delayed puberty plus anosmia, consistent with a diagnosis of Kallmann syndrome. Kallmann syndrome results from a failure of GnRH-secreting neurons to migrate from their origin in the olfactory placode (situated outside the central nervous system) to their normal anatomic location in the hypothalamus. Most often, the cause is a mutation in the KAL-1 gene or the fibroblast growth factor receptor-1 gene, which code for proteins required in this migration.

Patients with Kallmann syndrome classically have central hypogonadism and anosmia, although there may be other midline defects as well (eg, cleft lip or cleft palate). Most often, these patients present with delayed puberty. On physical examination, the testes are often just 1-2 mL in volume. There is usually some pubic hair because adrenarche occurs normally.

In the United States, delayed puberty is defined as the absence or incomplete development of secondary sexual characteristics by age 14 in boys and by age 12 in girls. Testicular enlargement is the first sign of puberty in boys, and breast enlargement is the first sign in girls. The initiation of puberty and the maintenance of secondary sexual characteristics and fertility require the coordinated efforts of the hypothalamus, pituitary, and gonads. Delayed puberty can result from a derangement anywhere in this axis.

(Choices B, C, D, and E) These pathways represent normal feedback loops between the testes and the

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puberty in boys, and breast enlargement is the first sign in girls. The initiation of puberty and the maintenance of secondary sexual characteristics and fertility require the coordinated efforts of the hypothalamus, pituitary, and gonads. Delayed puberty can result from a derangement anywhere in this axis.

(Choices B, C, D, and E) These pathways represent normal feedback loops between the testes and the hypothalamus and pituitary. Pituitary follicle-stimulating hormone (FSH) stimulates proliferation of the seminiferous tubules and spermatogenesis. The seminiferous tubules produce inhibin, which feeds back to inhibit pituitary FSH secretion. Luteinizing hormone from the pituitary stimulates the interstitial Leydig cells to produce testosterone, which also participates in feedback inhibition.

Educational objective:
In Kallmann syndrome, there is an absence of GnRH secretory neurons in the hypothalamus due to defective migration from the olfactory placode. These patients have central hypogonadism and anosmia, and often present with delayed puberty.

Pathology	Endocrine, Diabetes & Metabolism	Kallmann syndrome
Subject	System	Topic

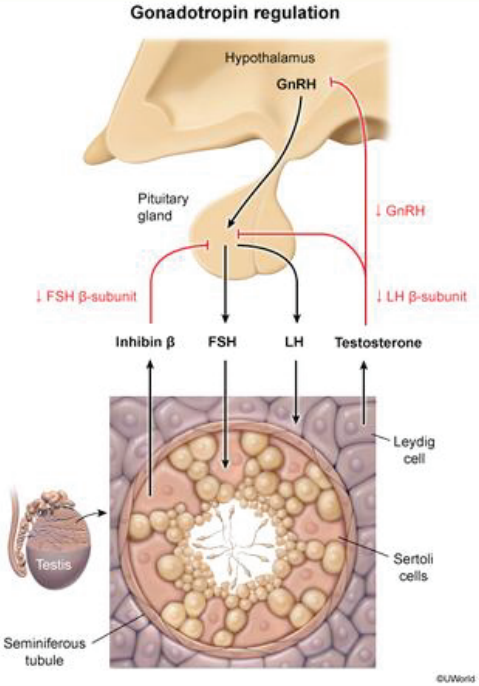
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A 55-year-old man comes to the emergency department due to progressive weakness and lethargy. The patient says that over the past 3 months he has been excessively thirsty and waking up several times at night to urinate. He has also lost 5 kg (11 lb) during this time despite no change in appetite. The patient has not seen a doctor in several years. Family history is significant for type 2 diabetes mellitus in his mother and father. Blood pressure is 108/60 mm Hg, and pulse is 98/min. BMI is 38 kg/m^2. Physical examination shows dry mucous membranes and poor skin turgor. Laboratory testing reveals a blood glucose concentration of 600 mg/dL. Serum beta-hydroxybutyrate is normal, and hemoglobin A1c is 14%. The patient is admitted, and intravenous fluids and insulin infusion are begun. The next day, his symptoms significantly improve, and the blood glucose levels normalize. In preparation for discharge, his insulin infusion is changed to a subcutaneous regimen that closely mimics the physiologic pattern of insulin release. This patient's insulin therapy was most likely transitioned to which of the following regimens?

A. Combination NPH insulin plus regular insulin twice daily

B. Insulin aspart before each meal

C. Insulin detemir twice daily

D. Insulin glargine once daily

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A. Combination NPH insulin plus regular insulin twice daily

B. Insulin aspart before each meal

C. Insulin detemir twice daily

D. Insulin glargine once daily

E. Insulin glargine once daily plus insulin lispro before each meal

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mother and father. Blood pressure is 108/60 mm Hg, and pulse is 98/min. BMI is 38 kg/m^2. Physical examination shows dry mucous membranes and poor skin turgor. Laboratory testing reveals a blood glucose concentration of 600 mg/dL. Serum beta-hydroxybutyrate is normal, and hemoglobin A1c is 14%. The patient is admitted, and intravenous fluids and insulin infusion are begun. The next day, his symptoms significantly improve, and the blood glucose levels normalize. In preparation for discharge, his insulin infusion is changed to a subcutaneous regimen that closely mimics the physiologic pattern of insulin release. This patient's insulin therapy was most likely transitioned to which of the following regimens?

A. Combination NPH insulin plus regular insulin twice daily (10%)
B. Insulin aspart before each meal (15%)
C. Insulin detemir twice daily (0%)
D. Insulin glargine once daily (1%)
E. Insulin glargine once daily plus insulin lispro before each meal (71%)

Correct

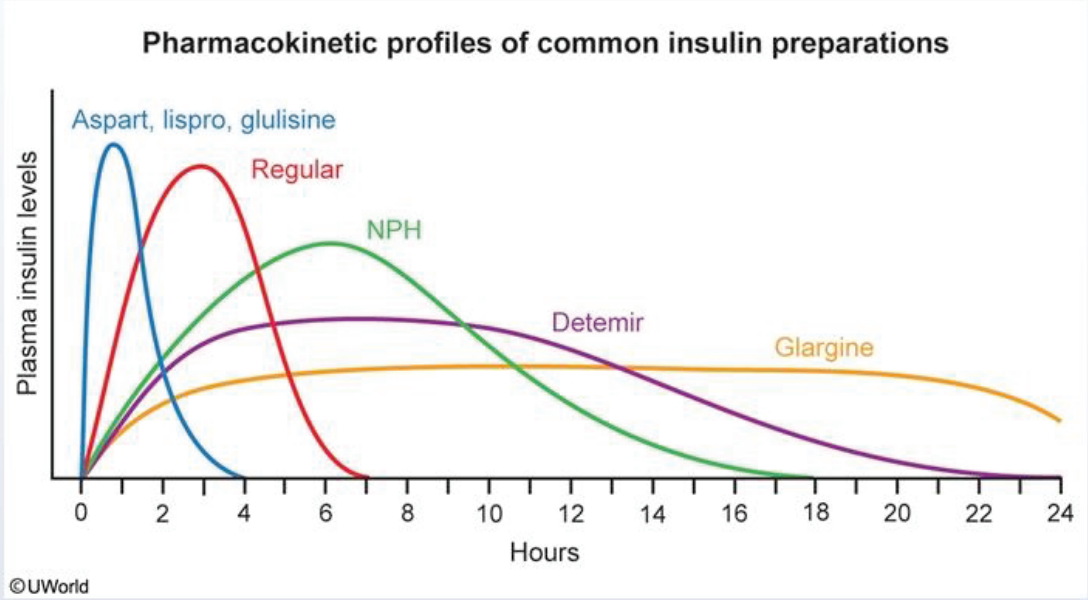
71%
Answered correctly

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Time Spent

11/22/2020
Last Updated

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Explanation



This patient has polyuria, polydipsia, weight loss, and risk factors for **type 2 diabetes mellitus** that include obesity and a positive family history; the striking elevation in hemoglobin A1c confirms the diagnosis. He

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This patient has polyuria, polydipsia, weight loss, and risk factors for **type 2 diabetes mellitus** that include obesity and a positive family history; the striking elevation in hemoglobin A1c confirms the diagnosis. He now has lethargy, dehydration (eg, dry mucous membranes), and severe hyperglycemia that is consistent with a **hyperosmolar hyperglycemic state**, a potential complication of untreated diabetes. He was appropriately managed with intravenous fluids and insulin and now needs to be transitioned to chronic insulin therapy.

Insulin is normally secreted continuously by pancreatic beta cells 24 hours a day (basal insulin secretion). Then, following meals, insulin secretion increases transiently to control the postprandial surge in blood glucose as dietary sugar and digested carbohydrates are absorbed in the intestine.

Physiologic insulin secretion can be approximated by a combination of long-acting and rapid-acting insulin analogs (ie, basal-bolus regimen). **Long-acting preparations** (eg, glargine) are released from the injection site continuously throughout the day and **replicate basal insulin** secretion. Concurrently, boluses of a **rapid-acting insulin** (eg, lispro) that is quickly absorbed are given with each meal to control **postprandial glucose elevations**. Alternately, an insulin pump can provide a steady supply of insulin throughout the day as well as mealtime dose increases.

(Choice A) A regimen using NPH insulin and regular insulin twice daily does not closely replicate

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(Choice A) A regimen using NPH insulin and regular insulin twice daily does not closely replicate physiologic insulin secretion. NPH is an intermediate-acting insulin that has a significant (and delayed) peak effect, increasing the risk of hypoglycemia between doses. In addition, regular insulin can polymerize at the injection site, causing a short delay in absorption leading to higher postprandial glucose levels.

(Choice B) Insulin aspart alone can replicate postprandial insulin secretion but does not provide basal insulin effect.

(Choices C and D) Insulin glargine alone provides a basal insulin effect, while insulin detemir, given once or twice daily, has a shorter duration of effect than glargine but can be used as basal insulin in some patients; however, neither provides appropriate mealtime coverage to control postprandial glucose.

Educational objective:

Physiologic insulin secretion can be approximated by a combination of long-acting and rapid-acting insulin analogs. Long-acting preparations (eg, glargine) are released from the injection site slowly throughout the day and replicate basal insulin secretion. Boluses of a rapid-acting insulin (eg, lispro) with quick absorption are given with meals to control postprandial glucose elevations.

References

- A review of basal-bolus therapy using insulin glargine and insulin lispro in the management of diabetes

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A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. If present, which of the following additional findings would be most specific to the underlying cause of this patient's hyperthyroidism?

A. Atrial fibrillation
B. Decreased bone mineral density
C. Heat intolerance
D. Skin thickening and induration over the shin
E. Tremor of the outstretched hands

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work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. If present, which of the following additional findings would be most specific to the underlying cause of this patient's hyperthyroidism?

A. Atrial fibrillation (4%)
B. Decreased bone mineral density (4%)
C. Heat intolerance (27%)
✓ D. Skin thickening and induration over the shin (58%)
E. Tremor of the outstretched hands (5%)

Correct
58%
01 min, 14 secs
09/12/2020

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This patient has symptomatic hyperthyroidism with elevated serum free thyroxine and suppressed TSH levels. The most common cause of hyperthyroidism is **Graves disease**, however, hyperthyroidism can also be due to other processes such as toxic adenoma, toxic multinodular goiter, and thyroiditis. This patient's positive serum assay for **thyrotropin receptor antibodies** (TRAb) confirms the diagnosis of Graves disease. TRAb bind and activate the TSH receptor, causing increased release of thyroid hormone by the thyroid gland, which is responsible for the general symptoms of hyperthyroidism (eg, fatigue, palpitations, weight loss, and insomnia).

In addition to the thyroid, the TSH receptor antigen is present on fibroblasts, adipocytes, and other tissues. **Thyroid dermopathy** is caused by stimulation of fibroblasts by TRAb and activated T-cells, leading to excess production of glycosaminoglycans and adipogenesis. This leads to induration and thickening of the skin over the shins (**pretibial myxedema**, as shown above). Graves ophthalmopathy occurs in a similar manner, with expansion of the retro-orbital tissues displacing the globe forward (proptosis). Because these processes are directly related to TRAb, they have a high specificity for Graves disease.

(Choices A, B, C, and E) Hyperthyroidism also causes a hypermetabolic/hyperadrenergic state that can present with heat intolerance, tremor, lid lag, tachycardia, or atrial fibrillation. In addition, increased bone

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Thyroid dermopathy is caused by stimulation of fibroblasts by TRAb and activated T-cells, leading to excess production of glycosaminoglycans and adipogenesis. This leads to induration and thickening of the skin over the shins (**pretibial myxedema**, as shown above). Graves ophthalmopathy occurs in a similar manner, with expansion of the retro-orbital tissues displacing the globe forward (proptosis). Because these processes are directly related to TRAb, they have a high specificity for Graves disease.

(Choices A, B, C, and E) Hyperthyroidism also causes a hypermetabolic/hyperadrenergic state that can present with heat intolerance, tremor, lid lag, tachycardia, or atrial fibrillation. In addition, increased bone turnover can lead to osteoporosis and increased fracture risk. However, these findings are not mediated by TRAb and can be seen in hyperthyroidism of any cause (eg, thyroiditis, toxic multinodular goiter).

Educational objective:

Pretibial myxedema and Graves ophthalmopathy are specific features of Graves disease. They are caused by an autoimmune response directed against the TSH receptor that results in the accumulation of glycosaminoglycans within the affected tissues.

References

- Thyroid dermopathy and acropachy.

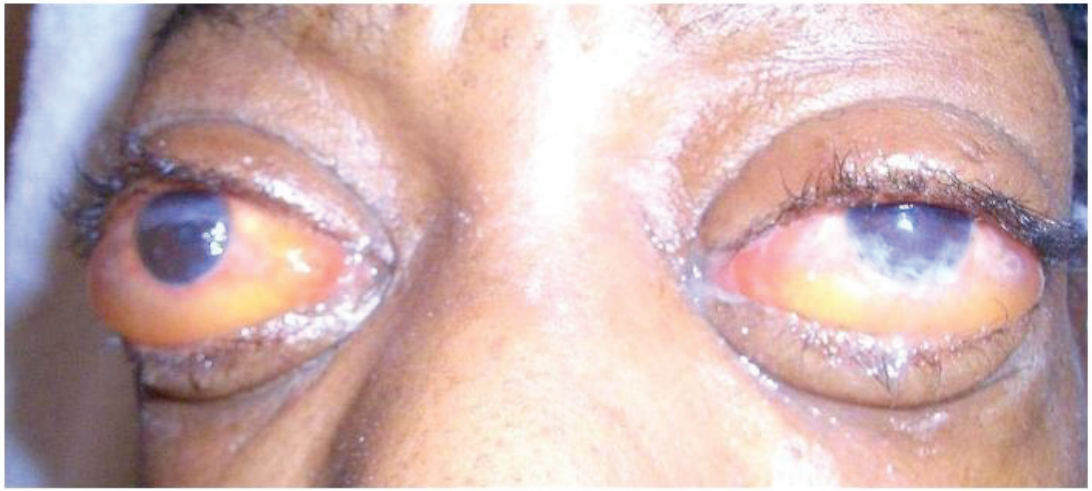
Pathophysiology Endocrine, Diabetes & Metabolism Hyperthyroidism

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Thyroid dermopathy is caused by stimulation of fibroblasts by TRAb and activated T-cells, leading to

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Pathophysiology | Endocrine, Diabetes & Metabolism | Hyperthyroidism

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A 54-year-old man comes to the office due to worsening fatigue, generalized weakness, and an unintentional 7-kg (15.4-lb) weight loss over the past several weeks. The patient has no prior medical conditions and takes no medications. He has a 40-pack-year history of smoking and does not use alcohol or illicit drugs. Blood pressure is 160/100 mm Hg and pulse is 80/min. Physical examination shows darkening of the skin in sun-exposed areas. There are scattered ecchymoses on the extremities. Mild proximal muscle weakness is present. Chest imaging reveals a 6-cm, irregular right lung mass with mediastinal lymphadenopathy. Which of the following is most likely responsible for the patient's current symptoms?

A. ACTH production from an ectopic site
B. Excess cortisol release from the lung mass
C. Excessive ACTH secretion from the pituitary
D. Hypothalamic dysfunction from metastatic process
E. Malignant invasion of the adrenal cortex

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- A. ACTH production from an ectopic site (85%)
- B. ~~Excess cortisol release from the lung mass~~ (3%)
- C. ~~Excessive ACTH secretion from the pituitary~~ (3%)
- D. Hypothalamic dysfunction from metastatic process (2%)
- E. Malignant invasion of the adrenal cortex (4%)

Correct

85%
Answered correctly

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Explanation

Common paraneoplastic syndromes associated with lung cancer	
Endocrine	• Syndrome of inappropriate antidiuretic hormone* • Parathyroid hormone-related protein secretion (hypercalcemia) • Ectopic ACTH production (Cushing syndrome)*
Neurologic	• Lambert-Eaton myasthenic syndrome* • Paraneoplastic cerebellar degeneration*
Musculoskeletal	• Hypertrophic osteoarthropathy (clubbing)

*Generally associated with small cell lung cancer.

This patient has fatigue, weakness, and weight loss associated with a suspicious **lung mass**. His hypertension, ecchymoses, and hyperpigmentation suggest **paraneoplastic hypercortisolism** (Cushing syndrome) due to **ectopic ACTH** secretion. As with primary adrenal insufficiency, excess ACTH secretion leads to hyperpigmentation, likely due to co-secretion of alpha-melanocyte-stimulating hormone (alpha-

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This patient has fatigue, weakness, and weight loss associated with a suspicious **lung mass**. His hypertension, ecchymoses, and hyperpigmentation suggest **paraneoplastic hypercortisolism** (Cushing syndrome) due to **ectopic ACTH** secretion. As with primary adrenal insufficiency, excess ACTH secretion leads to hyperpigmentation, likely due to co-secretion of alpha-melanocyte-stimulating hormone (alpha-MSH) (both ACTH and alpha-MSH are derived from pro-opiomelanocortin) and direct stimulation of the MC2R receptor on melanocytes by ACTH. Although patients with paraneoplastic hypercortisolism may have many of the typical metabolic features of cortisol excess (eg, hypertension, hyperglycemia, edema), **weight loss** is more common than classic Cushingoid central obesity.

Paraneoplastic hypercortisolism is most commonly associated with small cell lung cancer but can also be seen with other neuroendocrine tumors (eg, bronchial or pancreatic carcinoid). ACTH secreted by small cell lung cancer is not inhibited by high-dose exogenous corticosteroids (eg, dexamethasone), whereas pituitary ACTH secretion decreases via negative feedback.

(Choice B) Cortisol is produced by the zona fasciculata of the adrenal cortex, and autonomous cortisol production (ie, ACTH-independent hypercortisolism) is almost always due to a primary adrenal disorder (eg, adrenal adenoma). Regardless of the source, excess cortisol in a patient with intact hypothalamus-pituitary function suppresses ACTH and patients do not develop hyperpigmentation.

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Clinical features of Cushing syndrome

- **Central obesity** (eg, fat accumulation in the face [ie, moon face] & back of the neck [ie, buffalo hump])
- **Glucose intolerance**
- Hypertension
- Menstrual changes & decreased libido
- Skin atrophy
- Easy bruisability
- Hirsutism & acne (excess androgens)
- Proximal muscle weakness

New | Existing

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pituitary function suppresses ACTH and patients do not develop hyperpigmentation.

(Choice C) Given this patient's large lung mass and associated weight loss (instead of weight gain and central fat deposition), paraneoplastic ACTH secretion is more likely than an ACTH-producing pituitary adenoma (Cushing disease).

(Choice D) Metastasis to the hypothalamus would likely cause endocrine insufficiency resulting from a lack of trophic hormones to the anterior pituitary. Decreased production of corticotropin-releasing hormone would lead to central adrenal insufficiency, not hypercortisolism.

(Choice E) The adrenal glands are a common site of metastasis. If significant destruction of the adrenal cortical tissue occurs bilaterally, adrenal insufficiency may result. A subsequent increase of ACTH may cause hyperpigmentation; however, symptoms of adrenal insufficiency (eg, hypotension) would be expected, as opposed to the symptoms of cortisol excess seen in this patient.

Educational objective:
Paraneoplastic hypercortisolism, most commonly caused by small cell lung cancer, is due to ectopic ACTH secretion. Clinical features include hypertension, hyperglycemia, edema, and hyperpigmentation. Unlike nonparaneoplastic Cushing syndrome, central obesity is uncommon.

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A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patient unresponsive with no pulse, and she does not revive despite extensive cardiopulmonary resuscitation efforts. She had a prolonged history of systemic lupus erythematosus treated with multiple medications and was recently evaluated for progressive muscle weakness. Records from the patient's most recent office visit show an elevated blood pressure and examination findings of facial plethora, truncal obesity, and skin ecchymoses. She was also found to have mild hyperglycemia. Medical history included a left hip replacement for osteonecrosis of the femoral head 1 year ago. At autopsy, she is found to have an occluding thrombus in the left main coronary artery, which likely led to sudden cardiac death. Examination of this patient's adrenal glands is most likely to reveal which of the following findings?

A. Adrenocortical adenoma
B. Bilateral cortical atrophy
C. Diffuse cortical hyperplasia
D. Diffuse cortical hypertrophy
E. Nodular cortical hyperplasia

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A. Adrenocortical adenoma (8%)
B. Bilateral cortical atrophy (66%)
C. Diffuse cortical hyperplasia (15%)
D. Diffuse cortical hypertrophy (7%)
E. Nodular cortical hyperplasia (1%)

Correct

66%
Answered correctly

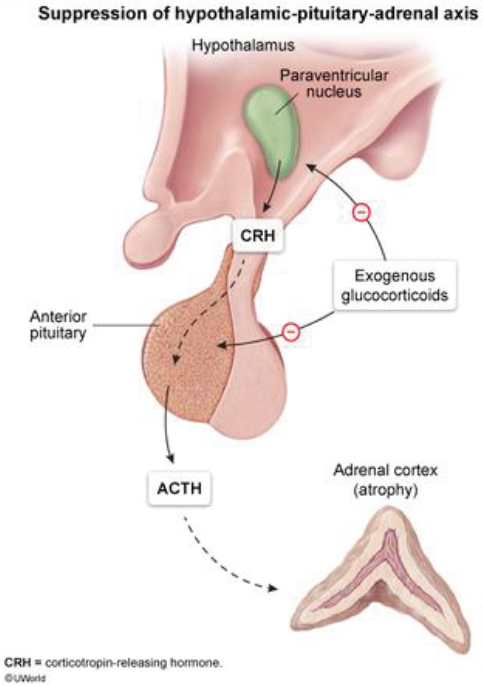
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CRH = corticotropin-releasing hormone.
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This patient has features of hypercortisolism, including hypertension, central obesity, muscular weakness, ecchymoses, and hyperglycemia. She most likely developed **iatrogenic Cushing syndrome** due to prolonged administration of glucocorticoids for management of systemic lupus erythematosus (SLE). **Chronic glucocorticoid use** can also cause osteonecrosis, and both Cushing syndrome and SLE itself can increase the risk for atherosclerosis and acute coronary events (as in this patient).

Exogenous glucocorticoid use **inhibits the entire hypothalamic-pituitary-adrenal axis**, leading to low levels of corticotropin-releasing hormone (CRH), ACTH, and endogenous cortisol. ACTH exerts a potent trophic (ie, growth promoting) effect on the adrenal zona fasciculata and reticularis; **long-term** suppression leads to **adrenocortical atrophy** (the zona glomerulosa is spared as angiotensin II is its primary trophic hormone). **Sudden cessation** of glucocorticoids after prolonged use can precipitate adrenocortical insufficiency and **adrenal crisis**.

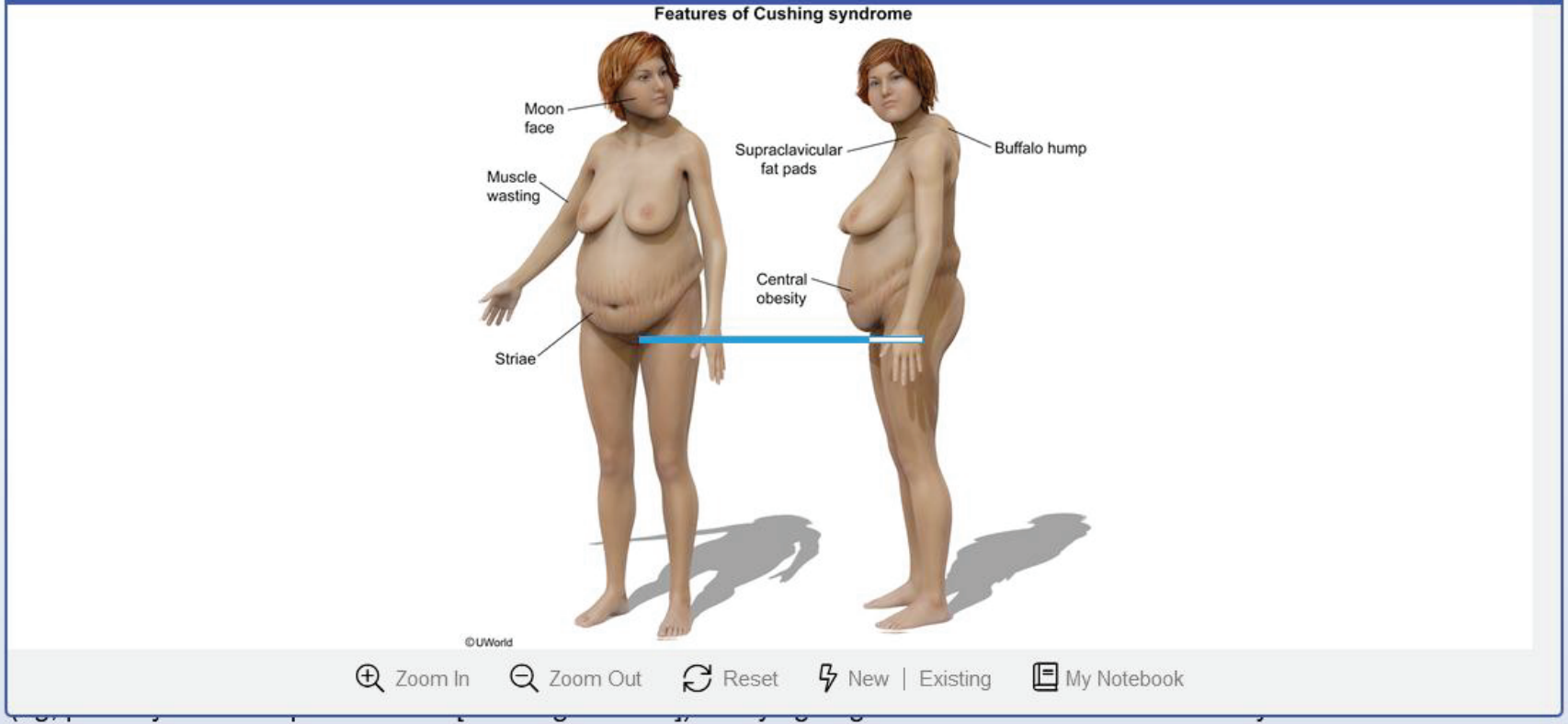
(Choice A) Endogenous Cushing syndrome can be caused by an autonomous cortisol-producing adrenal tumor. However, this patient's history is more suggestive of exogenous glucocorticoid use.

(Choices C, D, and E) Bilateral cortical hyperplasia and hypertrophy occurs in patients with ACTH excess (eg, pituitary corticotroph adenoma [Cushing disease]). Varying degrees of adrenocortical nodularity can

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CRH = corticotropin-releasing hormone.

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(Choice A) Endogenous Cushing syndrome can be caused by an autonomous cortisol-producing adrenal tumor. However, this patient's history is more suggestive of exogenous glucocorticoid use.

(Choices C, D, and E) Bilateral cortical hyperplasia and hypertrophy occurs in patients with ACTH excess (eg, pituitary corticotroph adenoma [Cushing disease]). Varying degrees of adrenocortical nodularity can also be seen. However, this patient was likely taking exogenous glucocorticoids, which would suppress ACTH release and lead to adrenocortical atrophy.

Educational objective:

Long-term use of supraphysiologic doses of glucocorticoids causes suppression of the hypothalamic-pituitary-adrenal axis, which in turn leads to bilateral adrenocortical atrophy involving the zona fasciculata and reticularis. Sudden cessation of the exogenous corticosteroids can precipitate adrenal crisis.

References

- Management issues with exogenous steroid therapy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

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A young Ashkenazi Jewish couple comes to the obstetrician because they are interested in conceiving a child. They are offered genetic screening because of the high rate of rare disease carriers within the population. Preconception genetic testing shows that both are carriers for sphingomyelinase deficiency, an autosomal recessive disorder. They are counseled about the 1 in 4 chance that their offspring will be affected by this disorder. The couple wants to know the clinical features of an affected child. Which of the following is most consistent with this condition?

A. Bone pain and pancytopenia
B. Dysostosis multiplex and corneal clouding
C. Neurodegeneration and hepatosplenomegaly
D. Neuropathic pain and angiokeratomas
E. Small stature and infertility

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A. ~~Bone pain and pancytopenia~~ (1%)

B. ~~Dysostosis multiplex and corneal clouding~~ (3%)

C. Neurodegeneration and hepatosplenomegaly (89%)

D. Neuropathic pain and angiokeratomas (3%)

E. ~~Small stature and infertility~~ (1%)

Correct

89%
Answered correctly

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Sphingolipidoses				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Fabry disease	XLR	α-Galactosidase A	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs disease		β-Hexosaminidase A	G_{M2} (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher disease		β-Glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia

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Niemann-Pick disease	AR	Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe disease		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration • Peripheral neuropathy

AR = autosomal recessive; **XLR** = X-linked recessive.

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Niemann-Pick disease is an **autosomal recessive** lysosomal storage disorder caused by **sphingomyelinase deficiency**. Sphingomyelinase is the enzyme responsible for sphingomyelin metabolism, and the excess sphingomyelin results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells accumulate in the liver and spleen **(hepatosplenomegaly)** and CNS **(hypotonia, neurodegeneration)**. After a period of normal development, infants do not attain new skills and lose previously acquired milestones (eg, sitting with support, head control, social smile). Retinal accumulation leads to a cherry-red macular spot. Death usually occurs by age 3.

Niemann-Pick disease and other rare genetic disorders (eg, Tay-Sachs disease, Gaucher disease, Bloom syndrome) are more common among the **Ashkenazi Jewish** population. The increased risk for rare and often life-threatening genetic mutations is attributed to the **founder effect**, or the loss of genetic variability within a group that historically conceived within their own community. An Ashkenazi Jewish couple should be offered **genetic counseling and testing** before they conceive a child.

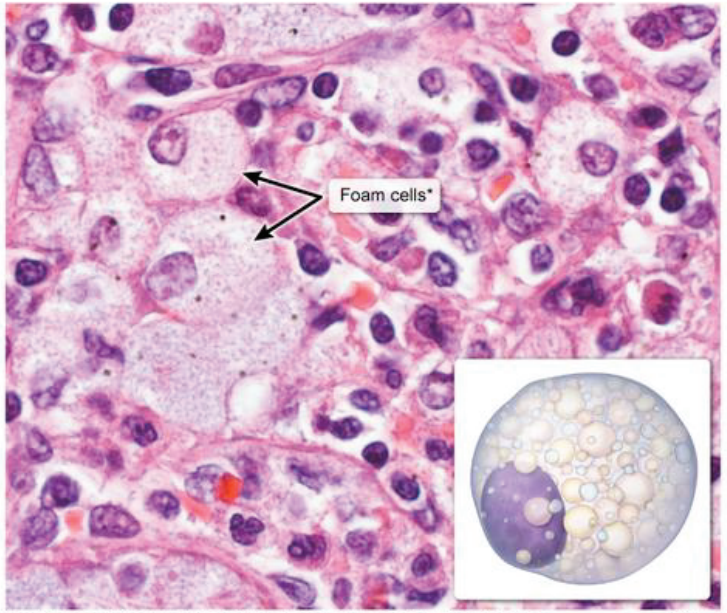
(Choice A) Gaucher disease, the most common genetic disorder among Ashkenazi Jews, is characterized by beta-glucocerebrosidase deficiency and glucocerebroside accumulation. Typical features include severe bone pain/osteopenia, pancytopenia, and hepatosplenomegaly.

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Niemann-Pick disease



*Macrophages with foamy cytoplasm due to sphingomyelin accumulation in lysosomes

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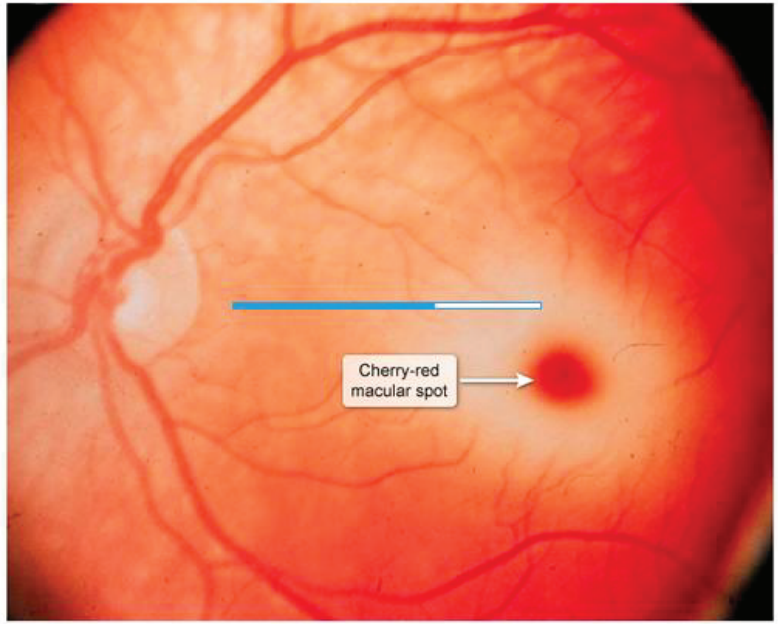
severe bone pain/osteopenia, pancytopenia, and hepatosplenomegaly.

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Cherry-red macular spot



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severe bone pain/osteopenia, pancytopenia, and hepatosplenomegaly.

(Choice B) Hurler syndrome is a mucopolysaccharidosis that leads to dysostosis multiplex (eg, enlarged skull, abnormally shaped ribs and vertebrae) and corneal clouding, which can cause blindness. This disorder is characterized by the accumulation of heparan sulfate and dermatan sulfate due to alpha-L-iduronidase deficiency.

(Choice D) In Fabry disease, alpha-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Disease manifestations include neuropathic pain and angiokeratomas in adolescence and multiorgan (eg, renal, cerebrovascular, cardiac) involvement in adulthood.

(Choice E) Small stature and infertility with a predisposition to malignancy and a classic sun-sensitive facial rash are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability.

Educational objective:
Niemann-Pick disease is an autosomal recessive disorder that is common in the Ashkenazi Jewish population. This disorder is characterized by sphingomyelinase deficiency and sphingomyelin accumulation, which cause hepatosplenomegaly and neurologic regression in infancy.

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A 67-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. She was diagnosed with diabetes 6 months ago. Lifestyle modification was initially advised, but the patient had no significant glycemic improvement. One month ago, the patient was started on metformin, to which she has been adherent; however, she has been experiencing abdominal discomfort and diarrhea attributed to the therapy. She has no other medical conditions. BMI is 28 kg/m^2. Physical examination is unremarkable. Laboratory tests show hemoglobin A1c is 8.2%. After further discussion, metformin is discontinued and glyburide is prescribed. Compared to metformin, this new therapy is most likely to increase the risk of which of the following?

A. Acute pancreatitis
B. Renal dysfunction
C. Symptomatic hypoglycemia
D. Vitamin B_{12} deficiency
E. Vulvovaginal candidiasis

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A. Acute pancreatitis (5%)
B. Renal dysfunction (3%)
✓ C. Symptomatic hypoglycemia (88%)
D. Vitamin B_{12} deficiency (0%)
E. Vulvovaginal candidiasis (1%)

Correct
88%
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Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss

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		• Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; K_{ATP} = ATP-sensitive potassium;

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Metformin is the preferred initial medication for most patients with type 2 diabetes due to its overall efficacy and lack of hypoglycemia when used in monotherapy. However, metformin can cause bothersome gastrointestinal effects (eg, nausea, diarrhea), which may be severe enough to warrant a change in therapy.

Sulfonylureas are second-line agents that are frequently used as add-on therapy or as a replacement for metformin. **Sulfonylureas** inhibit the **ATP-sensitive potassium channel** on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release** independent of blood glucose concentrations. Meglitinides (eg, repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

Sulfonylureas continue to stimulate insulin secretion, even when blood glucose levels are normal and can therefore cause **hypoglycemia**. Hypoglycemia due to sulfonylureas can be induced by exercise, missed meals, acute illness, or initiation of additional antidiabetic medications. Longer-acting sulfonylureas (eg, glyburide) are more prone to causing hypoglycemia than shorter-acting drugs (eg, glipizide).

(Choice A) Glucagonlike polypeptide-1 (GLP-1) regulates glucose by slowing gastric emptying and increasing insulin release. Pharmacologic GLP-1 agonists (eg, exenatide) lower blood glucose and promote weight loss. Acute pancreatitis is an uncommon but serious adverse effect

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excessive osmotic diuresis, but it is not a common adverse effect of sulfonylureas. However, preexisting renal impairment can increase the risk of hypoglycemia due to sulfonylureas and can increase the risk of lactic acidosis due to metformin.

(Choice D) Metformin can decrease absorption of vitamin B_{12}, leading to B_{12} deficiency in long-term use. Sulfonylureas do not have a significant effect on vitamin B_{12} metabolism.

(Choice E) SGLT2 inhibitors (eg, dapagliflozin) decrease renal reabsorption of glucose, leading to increased urinary glucose loss and lower blood glucose levels. The excess glucose in the urine can increase the risk of urinary tract infections and vulvovaginal candidiasis. They can also cause hypotension due to osmotic diuresis.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas stimulate insulin secretion, even when blood glucose levels are normal, which can lead to hypoglycemia.

Pharmacology Endocrine, Diabetes & Metabolism Diabetes mellitus

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(Choice E) SGLT2 inhibitors (eg, dapagliflozin) decrease renal reabsorption of glucose, leading to increased urinary glucose loss and lower blood glucose levels. The excess glucose in the urine can increase the risk of urinary tract infections and vulvovaginal candidiasis. They can also cause hypotension due to osmotic diuresis.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas stimulate insulin secretion, even when blood glucose levels are normal, which can lead to hypoglycemia.

Pharmacology Endocrine, Diabetes & Metabolism Diabetes mellitus

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A group of investigators is studying the regulation of catecholamine synthesis in response to severe stress. In the experiments, subject rats are randomly assigned to either an experimental or a control group. The experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

A. Catechol-O-methyl transferase
B. Dopa decarboxylase
C. Dopamine beta-hydroxylase
D. Monoamine oxidase
E. Phenylalanine hydroxylase
F. Phenylethanolamine-N-methyltransferase
G. Tyrosine hydroxylase

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experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

A. Catechol-O-methyl transferase (13%)
B. Dopa decarboxylase (11%)
C. Dopamine beta-hydroxylase (16%)
D. Monoamine oxidase (4%)
E. Phenylalanine hydroxylase (3%)
✓ F. Phenylethanolamine-N-methyltransferase (41%)
G. Tyrosine hydroxylase (10%)

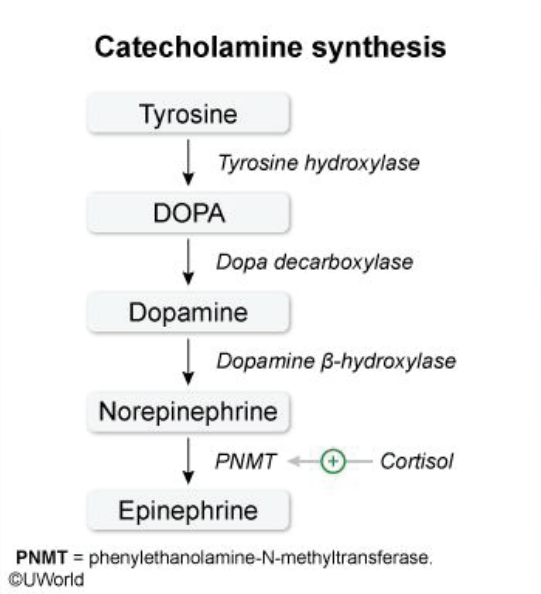
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The 3 main circulating catecholamines are dopamine, norepinephrine, and epinephrine. Norepinephrine and dopamine are produced in the central as well as the peripheral nervous system, whereas epinephrine is predominantly produced in the **adrenal medulla**. The first step in the synthesis of catecholamines is the conversion of tyrosine to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting

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step in the synthesis of catecholamines. DOPA is converted to dopamine by dopa decarboxylase **(Choice B)**, which is then converted to norepinephrine by dopamine beta-hydroxylase **(Choice C)**. In the adrenal medulla, norepinephrine is rapidly converted to epinephrine by **phenylethanolamine-N-methyltransferase** (PNMT).

Expression of PNMT in the adrenal medulla is upregulated by cortisol. Because the venous drainage of the adrenal cortex passes through the adrenal medulla, cortisol concentrations in the medulla can be very high, and PNMT is expressed at a high level. However, following **pituitary resection**, the loss of ACTH leads to decreased synthesis of cortisol in the adrenal cortex. The result is **decreased PNMT activity** and reduced conversion of norepinephrine to epinephrine.

(Choices A and D) Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible for inactivation of catecholamines. COMT converts epinephrine to metanephrine and norepinephrine to normetanephrine; MAO converts metanephrine and normetanephrine to vanillylmandelic acid.

(Choices E and G) Tyrosine required for the synthesis of catecholamines is obtained from either dietary intake or by conversion of phenylalanine by phenylalanine hydroxylase in the liver. Deficiency of phenylalanine hydroxylase enzyme causes phenylketonuria. Tyrosine hydroxylase deficiency impairs

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conversion of norepinephrine to epinephrine.

(Choices A and D) Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible for inactivation of catecholamines. COMT converts epinephrine to metanephrine and norepinephrine to normetanephrine; MAO converts metanephrine and normetanephrine to vanillylmandelic acid.

(Choices E and G) Tyrosine required for the synthesis of catecholamines is obtained from either dietary intake or by conversion of phenylalanine by phenylalanine hydroxylase in the liver. Deficiency of phenylalanine hydroxylase enzyme causes phenylketonuria. Tyrosine hydroxylase deficiency impairs catecholamine synthesis and causes infantile parkinsonism and progressive encephalopathy.

Educational objective:
Cortisol increases the conversion of norepinephrine to epinephrine in the adrenal medulla by increasing the expression of phenylethanolamine-N-methyltransferase.

References

- Stress-triggered changes in peripheral catecholaminergic systems.

Biochemistry Endocrine, Diabetes & Metabolism Pheochromocytoma

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A 55-year-old woman is diagnosed with breast cancer and undergoes breast-sparing mastectomy. The tumor margin did not show any invasion, and sentinel axillary lymph node biopsy was negative for nodal metastasis. The tumor was estrogen receptor and progesterone receptor positive but HER-2 negative. After discussion of management options, the patient is started on tamoxifen. While on this medication, she experiences hot flashes that come and go in waves and affect her sleep significantly. Which of the following conditions is the patient also likely to experience as a result of this therapy?

A. Decrease in bone mass
B. Decrease in HDL level
C. Endometrial hyperplasia
D. Fibroadenoma of the breast
E. Increase in LDL level

Submit

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A 55-year-old woman is diagnosed with breast cancer and undergoes breast-sparing mastectomy. The tumor margin did not show any invasion, and sentinel axillary lymph node biopsy was negative for nodal metastasis. The tumor was estrogen receptor and progesterone receptor positive but HER-2 negative. After discussion of management options, the patient is started on tamoxifen. While on this medication, she experiences hot flashes that come and go in waves and affect her sleep significantly. Which of the following conditions is the patient also likely to experience as a result of this therapy?

A. Decrease in bone mass (22%)
B. ~~Decrease in HDL level~~ (1%)
✓ C. Endometrial hyperplasia (72%)
D. Fibroadenoma of the breast (0%)
E. Increase in LDL level (2%)

Correct

72% Answered correctly

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Explanation

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer • Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only)

Tamoxifen and raloxifene are **selective estrogen receptor modulators** (SERMs). They interact with the estrogen receptor and have agonist or antagonist activity depending on the tissue. In breast tissue,

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Endometrial hyperplasia & carcinoma (tamoxifen only)

Tamoxifen and raloxifene are **selective estrogen receptor modulators** (SERMs). They interact with the estrogen receptor and have agonist or antagonist activity depending on the tissue. In breast tissue, tamoxifen has an anti-estrogenic effect, and it is used for adjuvant treatment of estrogen receptor-positive **breast cancer**. Tamoxifen reduces the risk of recurrent cancer as well as estrogen-dependent benign breast lesions (eg, fibroadenoma, cystic changes) **(Choice D)**.

In endometrial tissue, however, tamoxifen has a stimulatory effect and can lead to development of **endometrial hyperplasia** and endometrial cancer. This risk is not seen with raloxifene.

(Choice A) Tamoxifen and raloxifene act as partial estrogen receptor agonists in bone and can cause an increase in bone mineral density after menopause.

(Choices B and E) Tamoxifen has a favorable effect on serum lipids, with a decrease in total and LDL cholesterol and no significant change in HDL. Serum triglycerides may increase in some patients.

Educational objective:
Selective estrogen receptor modulators (eg, tamoxifen, raloxifene) are competitive inhibitors of estrogen binding to estrogen receptors. They can have agonist or antagonist effects depending on the specific tissue. Tamoxifen has an estrogenic effect on the uterus and can cause endometrial hyperplasia and

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breast cancer. Tamoxifen reduces the risk of recurrent cancer as well as estrogen-dependent benign breast lesions (eg, fibroadenoma, cystic changes) **(Choice D)**.

In endometrial tissue, however, tamoxifen has a stimulatory effect and can lead to development of **endometrial hyperplasia** and endometrial cancer. This risk is not seen with raloxifene.

(Choice A) Tamoxifen and raloxifene act as partial estrogen receptor agonists in bone and can cause an increase in bone mineral density after menopause.

(Choices B and E) Tamoxifen has a favorable effect on serum lipids, with a decrease in total and LDL cholesterol and no significant change in HDL. Serum triglycerides may increase in some patients.

Educational objective:
Selective estrogen receptor modulators (eg, tamoxifen, raloxifene) are competitive inhibitors of estrogen binding to estrogen receptors. They can have agonist or antagonist effects depending on the specific tissue. Tamoxifen has an estrogenic effect on the uterus and can cause endometrial hyperplasia and cancer.

References

- Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study.

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A 22-year-old man comes to the office for evaluation of a neck mass. He first noticed a small nodule in his lower neck 6 months ago, and it has progressively enlarged since that time. The patient has had no changes in weight and otherwise feels well. Medical history is notable only for seasonal allergies, and he takes no medications. Physical examination shows a 2-cm nodule in the right lobe of the thyroid. There are multiple 4- to 8-mm soft papules on the lips and tongue. The arm span exceeds his height and the patient has long fingers. Serum calcitonin levels are elevated. Which of the following is most likely to develop in this patient?

A. Episodic headache
B. Hypercalcemia
C. Hypoglycemic episodes
D. Peripheral vision loss
E. Recurrent peptic ulcers

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- A. Episodic headache (65%)
- B. Hypercalcemia (14%)
- C. Hypoglycemic episodes (5%)
- D. Peripheral vision loss (8%)
- E. Recurrent peptic ulcers (5%)

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Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular)

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This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular) cells. These findings, in association with mucosal neuromas and **marfanoid habitus** (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B** (MEN2B). MEN2 syndromes are caused by germline mutations of the ***RET*** proto-oncogene. MTC is present in nearly all patients with MEN2 and is usually more aggressive and occurs at an earlier age than sporadic MTC.

Pheochromocytomas develop in roughly half of patients with MEN2 syndromes and cause paroxysmal hypertension and tachycardia due to the intermittent secretion of catecholamines. The abrupt, severe increase in blood pressure can precipitate **episodic headaches** and is often accompanied by other symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to refractory peptic ulceration and diarrhea (Zollinger-Ellison syndrome). In rare cases, endocrine tumors of the pancreas in MEN1 secrete other hormones, such as insulin, which can cause hypoglycemia.

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symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to refractory peptic ulceration and diarrhea (Zollinger-Ellison syndrome). In rare cases, endocrine tumors of the pancreas in MEN1 secrete other hormones, such as insulin, which can cause hypoglycemia.

(Choice D) Pituitary tumors are present in 50% of patients with MEN1. Large pituitary tumors with suprasellar extensions are likely to cause peripheral vision loss.

Educational objective:
Multiple endocrine neoplasia type 2B is characterized by medullary thyroid cancer, pheochromocytomas, mucosal neuromas, and marfanoid habitus. Hyperparathyroidism is not a feature of this syndrome.

References

- 2012 European Thyroid Association guidelines for genetic testing and its clinical consequences in medullary thyroid cancer.
- Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma.

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A 34-year-old, previously healthy woman comes to the office due to irregular menstruation and a 4.5 kg (10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m^2. Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS
A.	↑	↑	↑
B.	↓	↑	↓
C.	↑	↓	↓
D.	Normal	Normal	↑
E.	↓	↓	↓

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(10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m^2. Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS	
✓ A.	↑	↑	↑	(79%)
B.	↓	↑	↓	(3%)
C.	↑	↓	↓	(14%)
D.	~~Normal~~	~~Normal~~	↑	(1%)
E.	↓	↓	↓	(0%)

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Explanation

Categorization of Cushing syndrome		
	Etiology	**Distinguishing findings**
ACTH-dependent	• Cushing disease (ACTH-secreting pituitary adenoma) • Ectopic ACTH secretion	• Hyperpigmentation • Hyperandrogenism (eg, hirsutism, oligo/amenorrhea) • ↑ ACTH
ACTH-independent	• Adrenal mass (adenoma or carcinoma) • Exogenous glucocorticoids	• ↓ ACTH

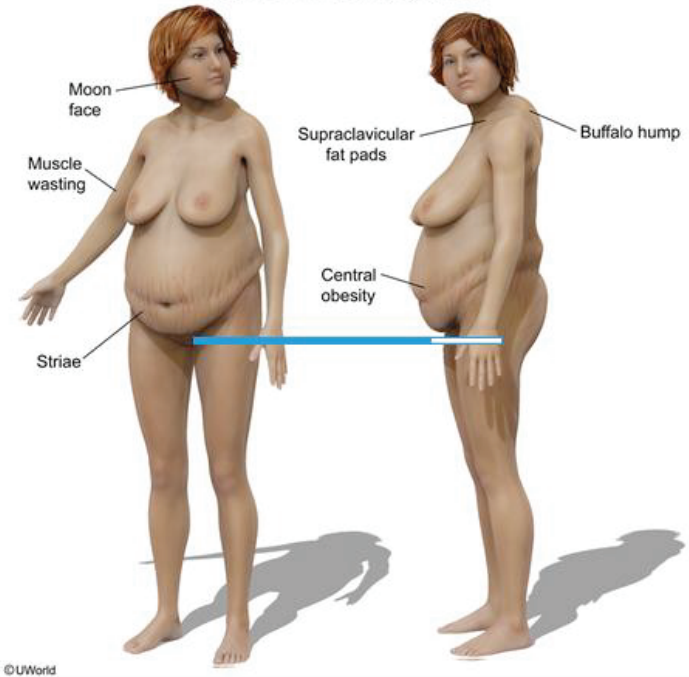
This patient with central obesity, proximal muscle weakness, striae, and hypertension has common features of cortisol excess (ie, Cushing syndrome). Other possible findings include hyperglycemia, dermal atrophy, and easy bruisability. Hypercortisolism can be confirmed on finding an elevated late-night salivary cortisol concentration or **increased 24-hour urine cortisol** excretion.

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Features of Cushing syndrome



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secretion causes identifiable clinical findings:

- **Hyperpigmentation:** Both ACTH and alpha-melanocyte-stimulating hormone (MSH) are derived from pro-opiomelanocortin, leading to cosecretion of alpha-MSH. ACTH also directly stimulates the MC2R receptor on melanocytes.
- Androgenization: ACTH stimulates production of adrenal androgens (eg, ↑**DHEAS** [dehydroepiandrosterone sulfate], androstenedione). This leads to **hirsutism**, **menstrual abnormalities**, and oily skin.

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

(Choice B) Primary adrenal insufficiency leads to decreased cortisol levels (and decreased urinary cortisol excretion) with a compensatory rise in ACTH. Hyperpigmentation may be present, but adrenal androgen production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not present.

(Choices C and E) ACTH-independent Cushing syndrome due to a cortisol-producing adrenal adenoma is characterized by increased urinary cortisol excretion with suppressed ACTH levels. Exogenous

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production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not present.

(Choices C and E) ACTH-independent Cushing syndrome due to a cortisol-producing adrenal adenoma is characterized by increased urinary cortisol excretion with suppressed ACTH levels. Exogenous glucocorticoids also cause suppression of ACTH, but with decreased production (and urinary excretion) of cortisol. Low cortisol excretion and ACTH levels are also seen in central adrenal insufficiency. Because ACTH is low in these states, patients do not have hyperpigmentation or hyperandrogenic features (eg, hirsutism).

(Choice D) Polycystic ovary syndrome is characterized by excessive ovarian production of androgens. Common clinical features include oligo/amenorrhea, obesity, and hirsutism. However, ACTH and cortisol production are unaffected, and hyperpigmentation is not seen.

Educational objective:
Cushing syndrome can be categorized as ACTH-dependent or ACTH-independent. Excess ACTH secretion in ACTH-dependent Cushing syndrome leads to hyperpigmentation. In addition to increased cortisol production, ACTH stimulates production of adrenal androgens (eg, testosterone, dehydroepiandrosterone sulfate) leading to hirsutism and menstrual irregularities.

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A 34-year-old woman comes to the office due to a 1 week history of mood swings, difficulty concentrating, and hand tremors. She also has pain at the front of her neck that radiates to her ears and is worse with swallowing. The patient initially attributed her symptoms to a flu-like illness that she had a few weeks earlier. She has no other medical conditions and takes no medications. Blood pressure is 140/80 mm Hg and pulse is 105/min. The thyroid gland is very tender on palpation. After initial laboratory testing, a thyroid scan is performed and reveals diffusely decreased radioiodine uptake. Erythrocyte sedimentation rate is 105 mm/hr. Which of the following pathological changes would be most likely on biopsy of this patient's thyroid gland?

A. Branching papillary structures with interspersed calcified bodies
B. Extensive stromal fibrosis extending beyond the thyroid capsule
C. Follicular hyperplasia with tall cells forming intrafollicular papillary projections
D. Mixed, cellular infiltration with occasional multinucleated giant cells
E. Mononuclear, parenchymal infiltration with well-developed germinal centers

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A 34-year-old woman comes to the office due to a 1 week history of mood swings, difficulty concentrating, and hand tremors. She also has pain at the front of her neck that radiates to her ears and is worse with swallowing. The patient initially attributed her symptoms to a flu-like illness that she had a few weeks earlier. She has no other medical conditions and takes no medications. Blood pressure is 140/80 mm Hg and pulse is 105/min. The thyroid gland is very tender on palpation. After initial laboratory testing, a thyroid scan is performed and reveals diffusely decreased radioiodine uptake. Erythrocyte sedimentation rate is 105 mm/hr. Which of the following pathological changes would be most likely on biopsy of this patient's thyroid gland?

A. Branching papillary structures with interspersed calcified bodies (2%)

B. Extensive stromal fibrosis extending beyond the thyroid capsule (6%)

C. Follicular hyperplasia with tall cells forming intrafollicular papillary projections (8%)

✓ D. Mixed, cellular infiltration with occasional multinucleated giant cells (62%)

✗ E. Mononuclear, parenchymal infiltration with well-developed germinal centers (19%)

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Explanation

Important causes of thyroiditis		
	Subacute granulomatous thyroiditis	**Hashimoto thyroiditis**
Clinical features	• Onset following a **viral illness** • **Painful** thyroid enlargement • Transient **hyperthyroid** symptoms	• **Autoimmune** etiology • **Painless** thyroid enlargement • Predominant **hypothyroid** features
Diagnostic testing	• ↑ ESR & CRP • ↓ Radioiodine uptake	• Positive **TPO antibody** • Variable radioiodine uptake
Pathology	• Inflammatory infiltrate with macrophages & **giant cells**	• Lymphocytic infiltrate with well-developed **germinal centers** • **Hürthle cells** (eosinophilic epithelial cells)

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **TPO** = thyroid peroxidase.

This patient with **painful** enlargement of the thyroid gland has **subacute granulomatous thyroiditis**

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This patient with **painful** enlargement of the thyroid gland has **subacute granulomatous thyroiditis** (SGT), also called de Quervain thyroiditis. SGT typically follows an acute **viral illness** and is thought to be due to a cross-reacting immune response against viral proteins or tissue antigens released during cellular injury. Patients may experience a **transient hyperthyroid phase** (elevated thyroxine [T4], suppressed TSH) due to release of stored thyroid hormone. Radioiodine uptake is decreased in SGT as the low TSH levels suppress synthesis of new thyroid hormone. The disease is self-limited and resolves in <6 weeks, although patients may have a brief hypothyroid phase before returning to a euthyroid state.

SGT is initially characterized by a neutrophilic infiltrate with microabscess formation, which, as the disease progresses, is replaced by a more generalized inflammatory infiltrate with macrophages and **multinucleated giant cells**. The inflammatory process is reflected by elevated serum acute-phase markers (eg, C-reactive protein, erythrocyte sedimentation rate).

(Choice A) Papillary thyroid cancer is characterized by branching papillary structures with concentric calcifications (psammoma bodies). This malignancy would typically present with nodular enlargement rather than acute pain and tenderness.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid gland that extends into surrounding tissues. The thyroid gland is hard and nontender.

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calcifications (psammoma bodies). This malignancy would typically present with nodular enlargement rather than acute pain and tenderness.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid gland that extends into surrounding tissues. The thyroid gland is hard and nontender.

(Choice C) Diffusely hyperplastic follicles with tall, crowded cells forming intrafollicular projections can be seen in Graves disease, which would show increased radioiodine uptake due to excessive TSH receptor stimulation.

(Choice E) Chronic lymphocytic (Hashimoto) thyroiditis is characterized by diffuse, painless thyroid enlargement, often with symptoms of hypothyroidism (eg, fatigue, cold intolerance). Biopsy reveals diffuse lymphocytic infiltration with formation of germinal centers.

Educational objective:
Subacute granulomatous (de Quervain) thyroiditis is characterized by painful thyroid enlargement and usually follows a viral illness. Biopsy shows a mixed inflammatory infiltrate with macrophages and multinucleated giant cells.

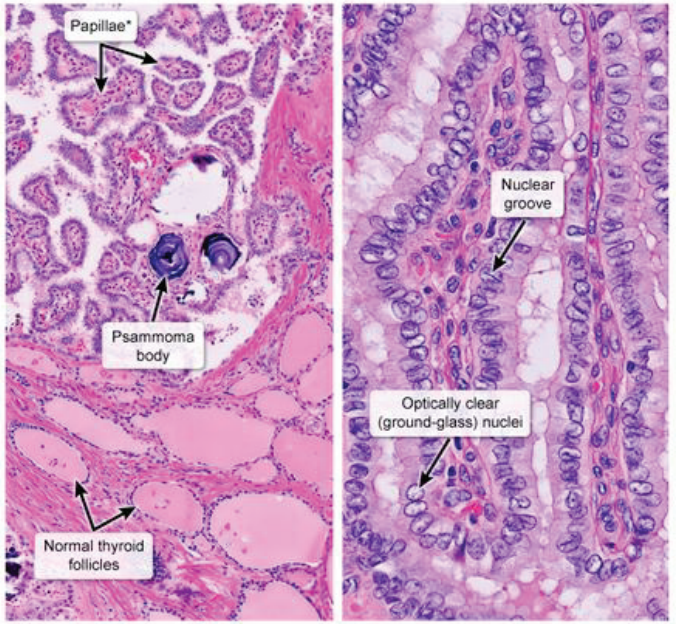
References

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Papillary thyroid carcinoma



*Fibrovascular cores lined by epithelial cells

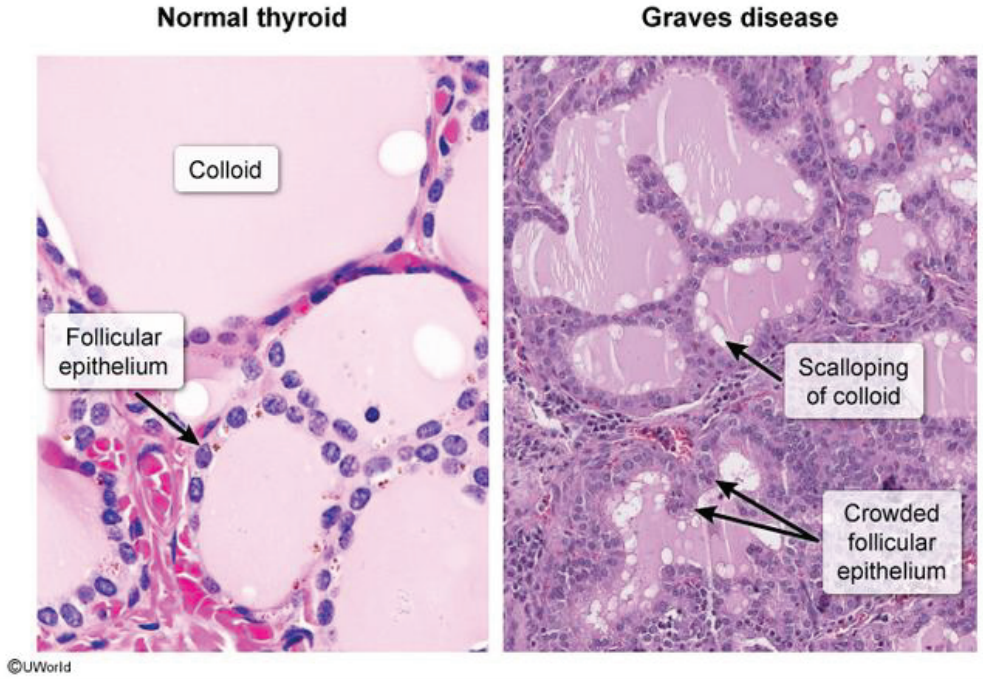
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multinucleated giant cells

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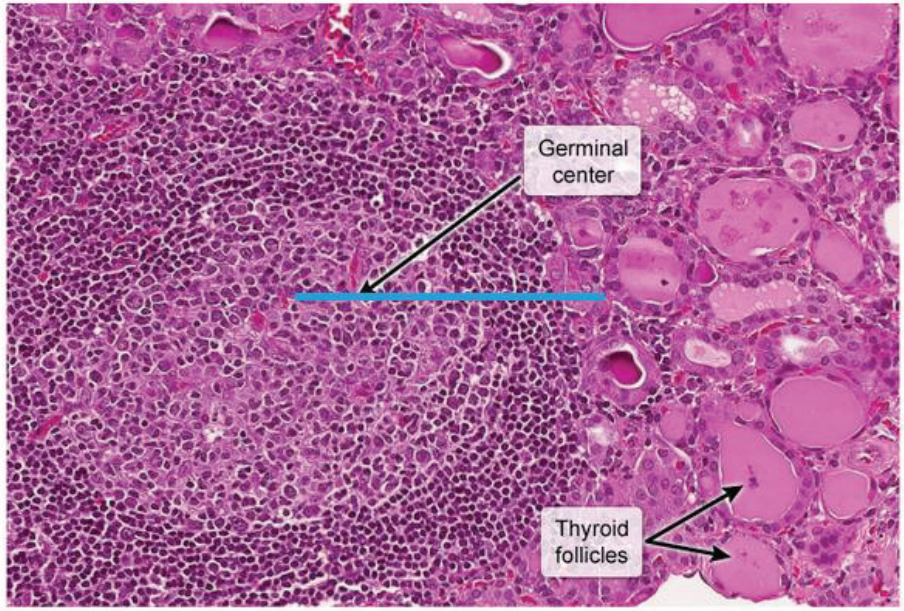
multinucleated giant cells

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Hashimoto thyroiditis



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multinucleated giant cells

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A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

A. 24-hour urinary cortisol excretion test
B. Dexamethasone suppression test
C. Fasting plasma glucose level
D. Serum iron studies
E. Serum triiodothyronine and thyroxine levels
F. Serum TSH level

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over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

- ✗ A. 24-hour urinary cortisol excretion test (3%)
- B. Dexamethasone suppression test (2%)
- C. ~~Fasting plasma glucose level~~ (0%)
- D. ~~Serum iron studies~~ (0%)
- E. Serum triiodothyronine and thyroxine levels (16%)
- ✓ F. Serum TSH level (75%)

Incorrect
Correct answer

75%
Answered correctly

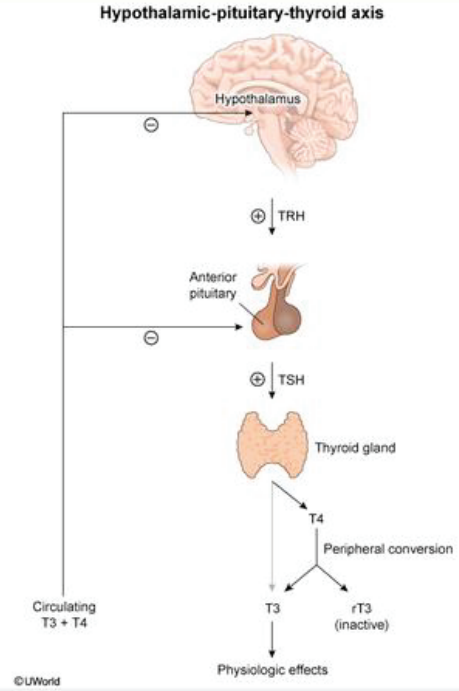
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09/28/2020
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This patient's symptoms (eg, fatigue, weight gain, constipation) and examination findings suggest **hypothyroidism**. Vital signs typically show bradycardia and hypertension (due to increased vascular resistance). Hypothyroidism can also cause slowed hair growth and alterations in hair growth cycles, leading to thinning of the scalp hair and lateral eyebrows. Slowed reuptake of calcium by the sarcoplasmic reticulum manifests as a delayed relaxation phase of deep tendon reflexes.

Most patients with hypothyroidism have **primary hypothyroidism** (ie, dysfunction within the thyroid gland). The thyroid releases thyroid hormones (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary. In turn, TSH secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses TSH and TRH via negative feedback, and **small changes in thyroid hormone** levels lead to **large changes in TSH** levels. As thyroid hormone production slows, TSH secretion increases rapidly to restore thyroid activity, often before T4 levels fall below standard laboratory reference ranges. Therefore, **serum TSH** is the **most sensitive** marker for primary hypothyroidism.

(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

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(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

(Choice C) Initial tests for diabetes mellitus include fasting glucose, hemoglobin A1c, and oral glucose tolerance tests. Diabetes can cause peripheral neuropathy (eg, paresthesias, loss of distal sensation, decreased ankle reflexes), but bradycardia, diastolic hypertension, and delayed relaxation of reflexes are more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

(Choice E) TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism. TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism), but this is a much less common cause of hypothyroidism (<5% of cases). In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction.

Educational objective:

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more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

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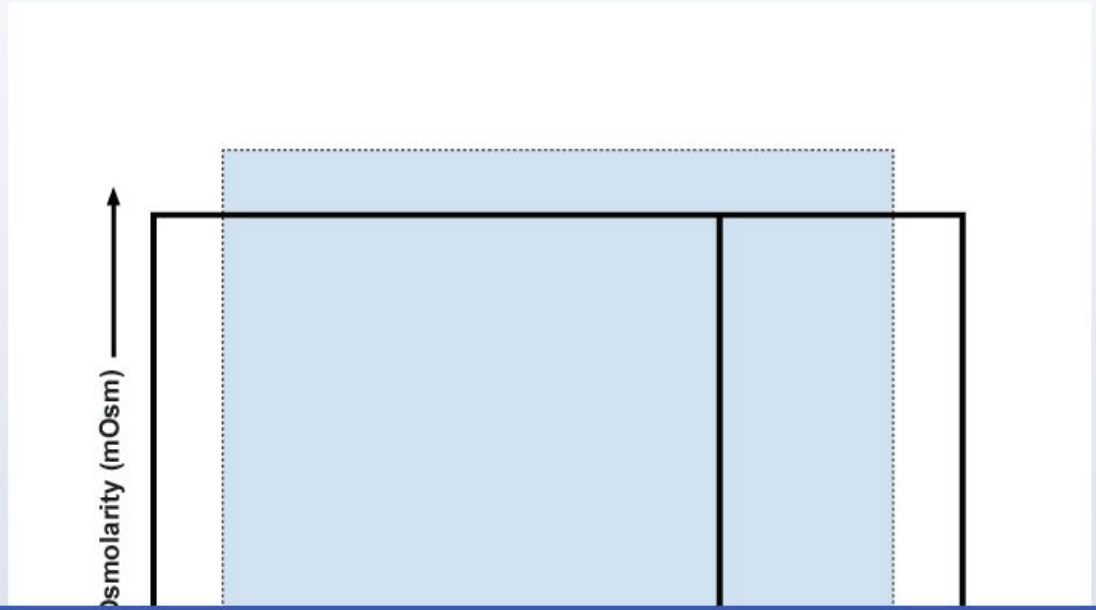
Educational objective:

The thyroid releases thyroid hormone (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary, which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses the secretion of TSH and TRH via negative feedback, and small changes in thyroid hormone levels cause large changes in TSH. Serum TSH is the most sensitive test for primary hypothyroidism.

References

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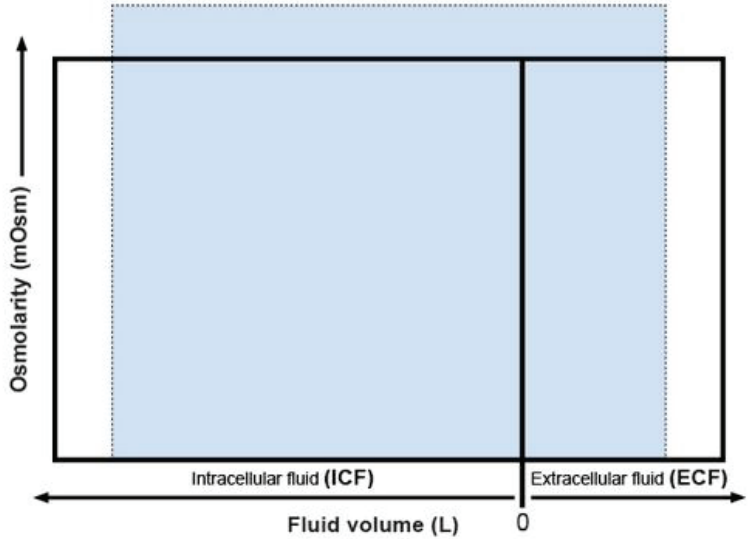
A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).



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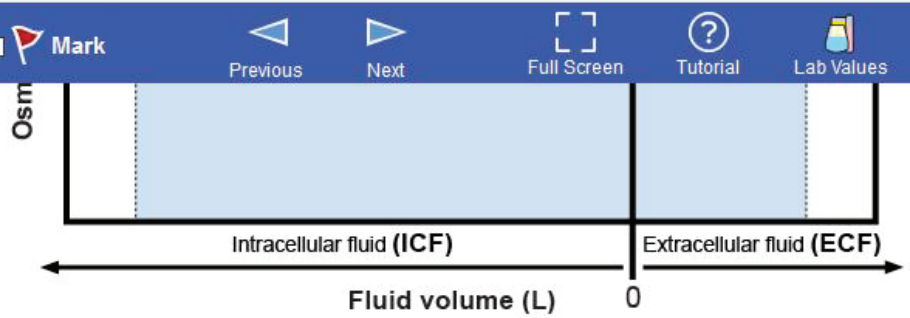
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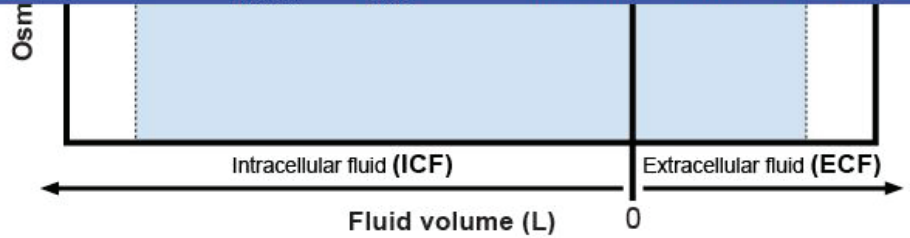
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Which of the following conditions is most likely to cause the findings shown in the image?

A. Acute gastrointestinal hemorrhage
B. Adrenal insufficiency
C. Diabetes insipidus
D. Hypertonic saline infusion
E. Primary polydipsia

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Which of the following conditions is most likely to cause the findings shown in the image?

A. ~~Acute gastrointestinal hemorrhage~~ (17%)
B. Adrenal insufficiency (7%)
C. Diabetes insipidus (55%)
D. Hypertonic saline infusion (14%)
E. Primary polydipsia (3%)

Correct

55%

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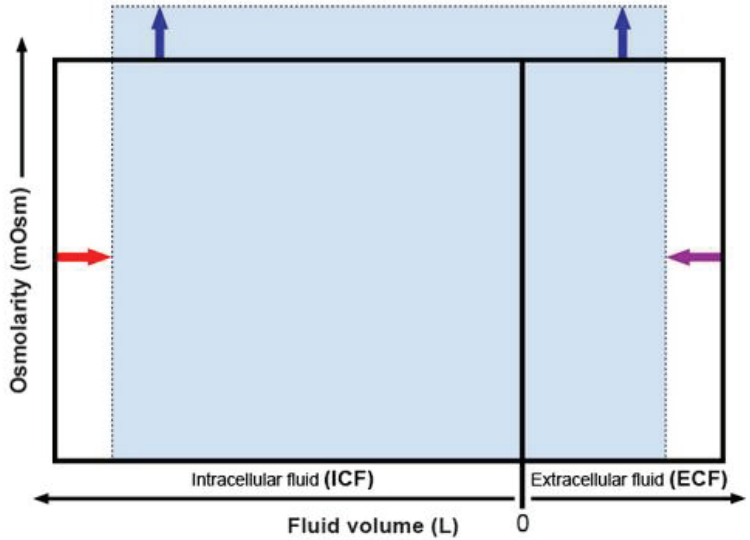
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Diabetes insipidus (DI)

Hyperosmotic volume contraction

↑Osm ↓ICF ↓ECF



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The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those compartments (y-axis).

This patient's recent **head trauma** is consistent with **central diabetes insipidus** due to hypothalamic/pituitary damage. The resulting decrease in vasopressin secretion leads to **excessive free water excretion** by the kidneys, causing **hyperosmotic volume contraction**. This condition occurs when the loss of free water exceeds the loss of electrolytes, resulting in **increased osmolarity** and **contracted volumes** in both the **ICF and ECF** compartments. Hyperosmotic volume contraction can occur in the setting of diabetes insipidus, decreased fluid intake (dehydration), and with profuse sweating (due to the hypotonic nature of sweat).

(Choice A) Acute gastrointestinal hemorrhage (or diarrhea) would cause an isotonic loss of ECF volume, with no effects on osmolarity or ICF volume. This is referred to as isosmotic volume contraction.

(Choice B) The lack of aldosterone in adrenal insufficiency causes loss of NaCl with ECF volume depletion (hyposmotic volume contraction). The low osmolarity of the ECF results in shifting of free water into the ICF compartment, causing ICF expansion.

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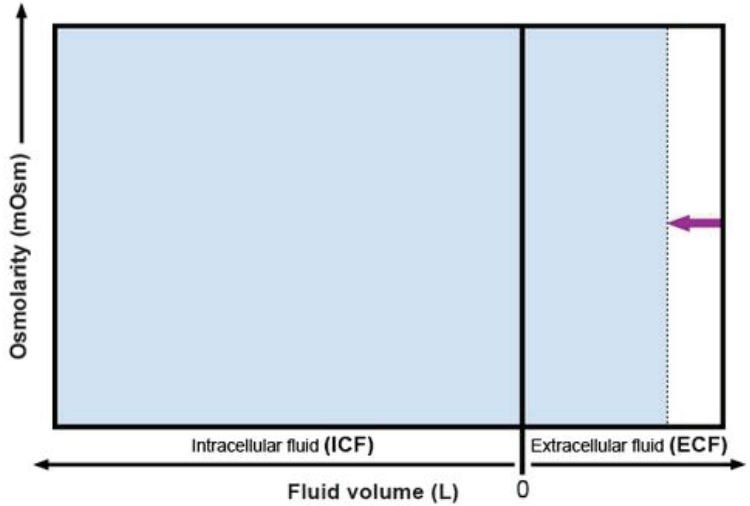
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GI hemorrhage (or diarrhea)

Loss of isotonic fluid

No change Osm Normal ICF ↓ECF



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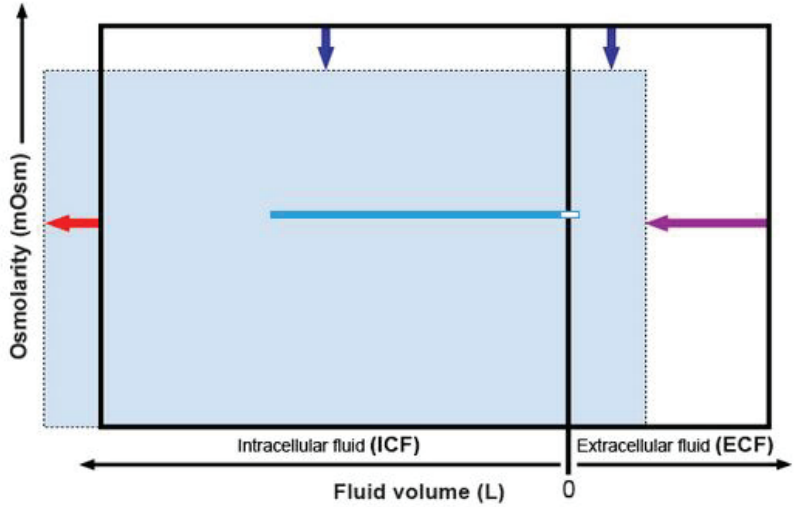
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Adrenal insufficiency

Hypertonic loss of Na^+

↓Osm ↑ICF ↓ECF



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depletion (hyposmotic volume contraction). The low osmolarity of the ECF results in shifting of free water into the ICF compartment, causing ICF expansion.

(Choice D) Infusion of large amounts of hypertonic saline leads to hypertonic volume expansion. Both the volume and osmolarity of the ECF are increased. The high osmolarity of the ECF leads to shifting of water from the ICF, further increasing the ECF volume.

(Choice E) Primary polydipsia (excessive water consumption) and SIADH (inappropriately high vasopressin levels) both cause retention of free water in the body. This leads to expansion of the ICF compartment and a decrease in the osmolarity of both compartments (hyposmotic volume expansion). Expansion of the ECF compartment is limited in these conditions due to compensatory secretion of aldosterone and natriuretic peptides, which help to normalize the extracellular fluid volume. Thus, affected patients are clinically euvolemic.

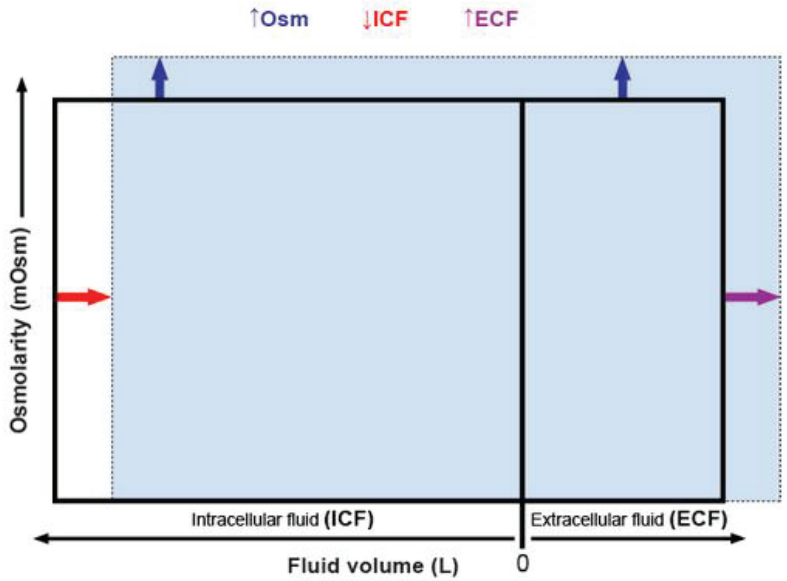
Educational objective:
Volume contraction and expansion can be divided into isosmotic, hyposmotic, and hyperosmotic states. Hyperosmotic volume contraction is caused by a loss of free water (with retention of electrolytes). It can occur in patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

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Hypertonic saline infusion



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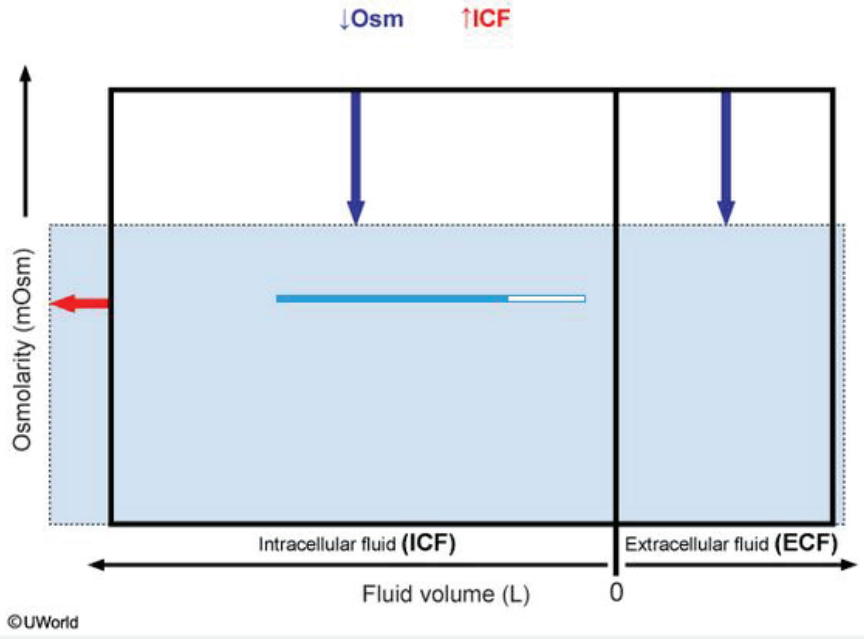
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Primary polydipsia & SIADH



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A 24-year-old postpartum woman comes to the office for follow-up of gestational diabetes. The patient was diagnosed with gestational diabetes mellitus during routine screening at 28 weeks gestation; she was treated with dietary modification and exercise and required insulin briefly. Since delivery 12 weeks ago, she has continued to follow dietary recommendations, and her blood glucose has been fairly well controlled without insulin. The patient has fasting blood glucose levels of 100-120 mg/dL. Medical history is otherwise unremarkable. Family history is significant for diabetes mellitus in her mother and gestational diabetes in her sister. Vital signs are within normal limits. BMI is 22 kg/m^2. Physical examination shows no abnormalities. Her gestational diabetes and fasting hyperglycemia are suspected to be genetically predisposed. This patient's condition is most likely caused by reduced activity of which of the following enzymes?

A. Aldolase A
B. Enolase
C. Glucokinase
D. Lactate dehydrogenase
E. Phosphofructokinase

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A. Aldolase A
B. Enolase
C. Glucokinase
D. Lactate dehydrogenase
E. Phosphofructokinase
F. Pyruvate carboxylase
G. Pyruvate kinase

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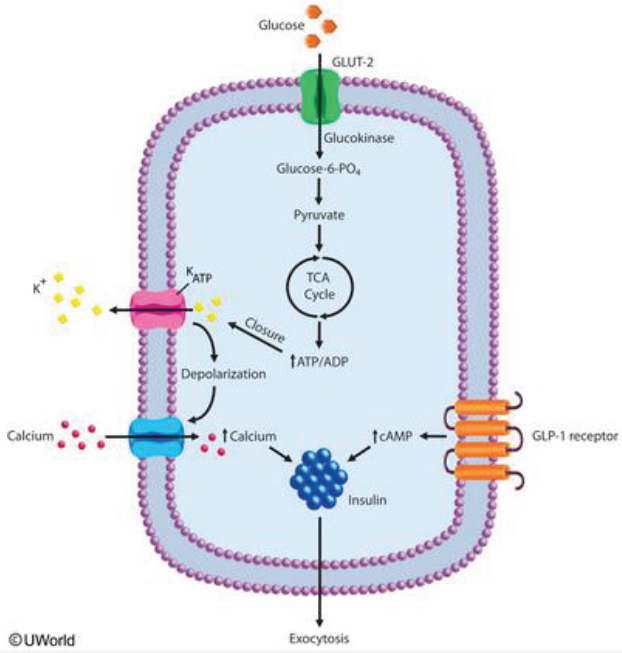
- A. Aldolase A (3%)
- B. Enolase (1%)
- ✓ C. Glucokinase (57%)
- D. Lactate dehydrogenase (2%)
- E. Phosphofructokinase (22%)
- F. Pyruvate carboxylase (6%)
- G. Pyruvate kinase (5%)

Correct 57% 03 mins, 19 secs 11/09/2020

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Pancreatic beta cell function



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Exocytosis

Glucose-induced insulin release from pancreatic beta cells requires the following steps:

1. Glucose enters the beta cell through glucose transporter type 2 (GLUT-2).
2. Glucose is metabolized by glucokinase to glucose-6-phosphate.
3. Glucose-6-phosphate enters glycolysis to produce ATP.
4. Increased ATP levels causes closure of ATP-sensitive potassium (K_{ATP}) channels.
5. Depolarization of beta cells triggers opening of voltage-dependent calcium channels.
6. Influx of calcium causes insulin release.

Glucokinase has a lower glucose affinity than other hexokinases, which allows it to limit the rate of glucose entry into the glycolytic pathway based on blood glucose levels. It therefore functions as a **glucose sensor** for beta cells in controlling insulin release.

Heterozygous mutations of the glucokinase gene that decrease the activity or affinity of the enzyme cause a decrease in beta cell glucose metabolism, leading to reduced ATP formation and insulin secretion at any given glucose level. Glucokinase mutations are one cause of **maturity-onset diabetes of the young (MODY)**, an autosomal dominant disorder characterized by **mild hyperglycemia** that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus,

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given glucose level. Glucokinase mutations are one cause of **maturity-onset diabetes of the young (MODY)**, an autosomal dominant disorder characterized by **mild hyperglycemia** that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus, patients with MODY are typically younger and nonobese, and the condition is **nonprogressive**, even without treatment.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia because red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenesis pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:
Insulin release by pancreatic beta cells is stimulated by increased glucose metabolism and ATP

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(Choice F) Pyruvate carboxylase, one of the gluconeogenesis pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:

Insulin release by pancreatic beta cells is stimulated by increased glucose metabolism and ATP production. Glucokinase functions as a glucose sensor in pancreatic beta cells by controlling the rate of glucose entry into the glycolytic pathway. Mutations in the glucokinase gene lead to a state in which higher glucose levels are required to stimulate insulin secretion and are a cause of maturity-onset diabetes of the young.

References

- Glucokinase MODY and implications for treatment goals of common forms of diabetes.

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A 40-year-old woman is hospitalized due to a femoral neck fracture that occurred when she slipped while stepping out of the bathtub. The patient was diagnosed with a prolactinoma 3 years ago during evaluation of amenorrhea, but she refused medical or surgical treatments. The tumor is being monitored closely and has not increased in size or caused any visual symptoms. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. She has 3 healthy children and no significant family history. The underlying mechanism for this patient's susceptibility to fracture is most likely to cause which of the following additional manifestations?

A. Hand tremors
B. Kidney stones
C. Stomach ulcers
D. Swallowing difficulty
E. Vaginal dryness

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A. Hand tremors (5%)
B. Kidney stones (19%)
C. Stomach ulcers (2%)
D. Swallowing difficulty (0%)
E. Vaginal dryness (70%)

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Complications of prolactinoma	
Hyperprolactinemia	• **Premenopausal women:** Galactorrhea, estrogen deficiency (oligo/amenorrhea, decreased bone density, vaginal atrophy) • **Men:** Infertility, decreased libido, impotence • **Children/adolescents:** Delayed puberty, growth impairment
Mass-effect symptoms	• Headache • Visual field defects • Suppression of other pituitary hormones

Prolactinomas are the most common pituitary tumors. High levels of circulating prolactin, a hormone involved in milk production, result in galactorrhea (nonlactational milk production) and infertility in premenopausal women. Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for

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premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor

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symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However, most prolactinomas are sporadic and not associated with MEN1. In addition, MEN1 is rare, and this patient's lack of a significant family history makes it even less likely.

Educational objective:

In patients with prolactinoma, high levels of circulating prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH and subsequent hypogonadism, anovulation, and amenorrhea. The resulting estrogen deficiency can cause osteoporosis with an increased risk for fragility fractures, and lead to vaginal dryness and atrophy.

References

- Hyperprolactinemia: pathophysiology and therapeutic approach.

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A 6-year-old girl is brought to the office for evaluation of short stature. Her parents have noticed that she bears little resemblance to her 2 older siblings. The patient's mother and father are 172.5 cm (5'8") and 183 cm (6') tall, respectively. On physical examination, the patient's height is 3 standard deviations below the mean for her age. Other findings include low-set ears, a high arched palate, a webbed neck, and cubitus valgus. Chromosomal analysis reveals a 45,XO karyotype. The patient is started on a medication to improve growth and normalize her height. Which of the following intracellular pathways is stimulated by the medication used in this patient?

A. Binding of activated receptors to DNA to modify transcription
B. Cyclic AMP-Protein kinase A pathway
C. Diacylglycerol-Protein kinase C pathway
D. Inositol triphosphate–calcium–calmodulin pathway
E. JAK-STAT pathway

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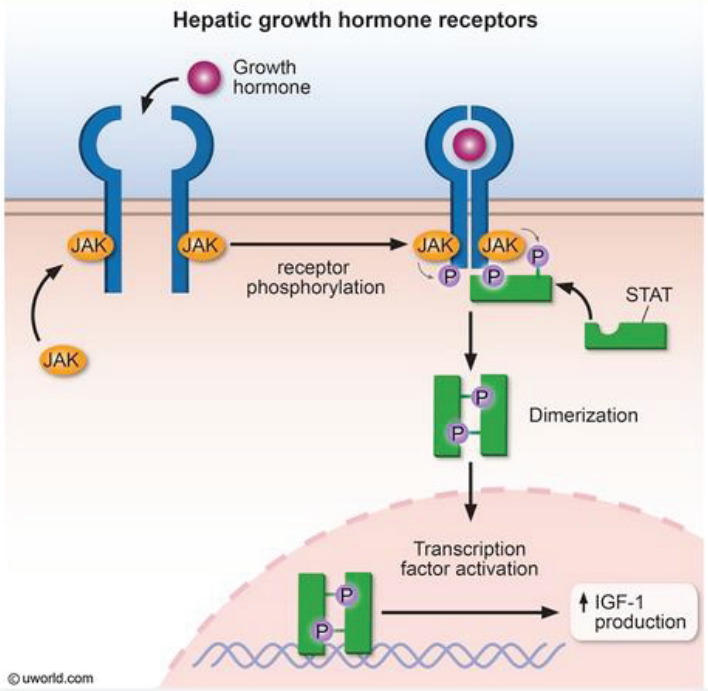
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A. Binding of activated receptors to DNA to modify transcription (22%)
B. Cyclic AMP-Protein kinase A pathway (13%)
C. Diacylglycerol-Protein kinase C pathway (3%)
D. Inositol triphosphate–calcium–calmodulin pathway (5%)
E. JAK-STAT pathway (54%)

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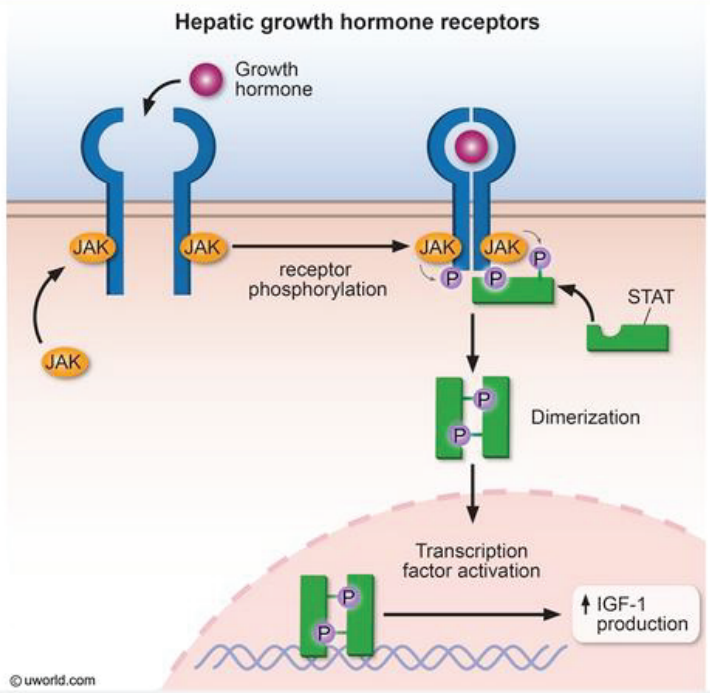
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Hepatic growth hormone receptors

Exhibit Display



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This patient with a 45,XO karyotype has Turner syndrome. Individuals with this condition are typically treated with **growth hormone** (GH) when growth failure becomes evident, leading to normalization of height in most patients.

GH promotes growth by acting on the cell surface receptors that stimulate production of insulin-like growth factor-1 (IGF-1), primarily in the liver. One GH molecule binds to 2 receptors on the cell surface, leading to activation of **Janus kinase (JAK)**, a **nonreceptor tyrosine kinase**. JAK subsequently phosphorylates several tyrosine residues in the intracellular domain of the GH receptor. These phosphorylated tyrosine residues function as docking sites for **STAT** (**signal transducer and activator of transcription**). Once STAT is recruited to the receptor, it is also phosphorylated by JAK. STAT then dimerizes and translocates to the nucleus, where it induces *IGF-1* gene transcription by binding to the promoter region. Other molecules that use the JAK-STAT pathway include cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF).

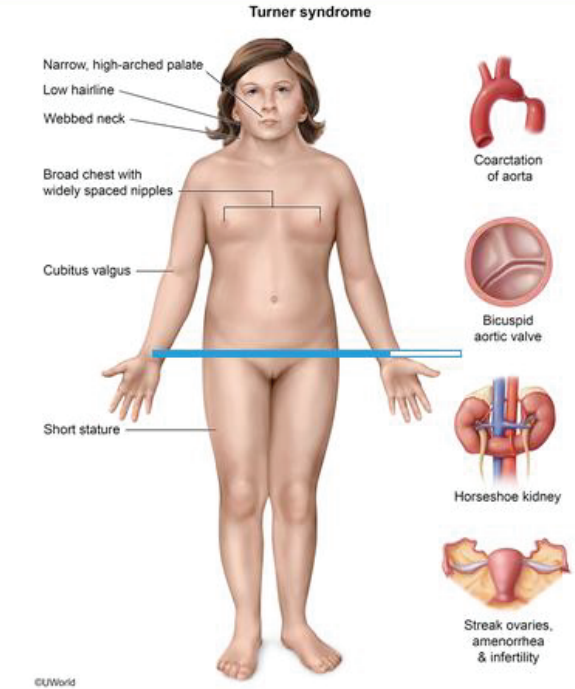
(Choice A) Steroid and thyroid hormones bind to intracellular receptors. Once these receptors are activated, they subsequently bind to the promoter region of target genes to modify transcription.

(Choice B) Several hormones (eg, PTH, ACTH, TSH, ADH [V2 receptor]) activate adenylyl cyclase after binding to G protein-coupled receptors on the cell membrane. Adenylyl cyclase converts ATP to cyclic

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binding to G protein-coupled receptors on the cell membrane. Adenylyl cyclase converts ATP to cyclic

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factors (eg, erythropoietin, G-CSF).

(Choice A) Steroid and thyroid hormones bind to intracellular receptors. Once these receptors are activated, they subsequently bind to the promoter region of target genes to modify transcription.

(Choice B) Several hormones (eg, PTH, ACTH, TSH, ADH [V2 receptor]) activate adenylyl cyclase after binding to G protein-coupled receptors on the cell membrane. Adenylyl cyclase converts ATP to cyclic AMP, which subsequently activates protein kinase A.

(Choices C and D) Various hormones (eg, GnRH, TRH, angiotensin II, ADH [V1 receptor]) function by binding to G protein-coupled receptors that activate phospholipase C. Activated phospholipase C hydrolyzes phosphatidylinositol bisphosphate to inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes calcium from the endoplasmic reticulum, and DAG directly activates protein kinase C.

Educational objective:
Growth hormone binds to cell surface receptors, leading to intracellular activation of the JAK-STAT pathway. Cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF) also use this pathway.

References

- The role of STAT proteins in growth hormone signaling.

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A 16-year-old boy is brought to the emergency department because of confusion, fatigue, and abdominal pain. He has also experienced excessive thirst and polyuria during the last 3 weeks. His past medical history is insignificant. Family history is unremarkable. Urine dipstick is positive for glucose and ketones. Which of the following factors most likely contributed to the development of this patient's condition?

A. Abdominal fat distribution
B. Excessive body weight
C. Genetic defects in insulin secretion
D. Islet amyloid deposition
E. Islet leukocytic infiltration

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A 16-year-old boy is brought to the emergency department because of confusion, fatigue, and abdominal pain. He has also experienced excessive thirst and polyuria during the last 3 weeks. His past medical history is insignificant. Family history is unremarkable. Urine dipstick is positive for glucose and ketones. Which of the following factors most likely contributed to the development of this patient's condition?

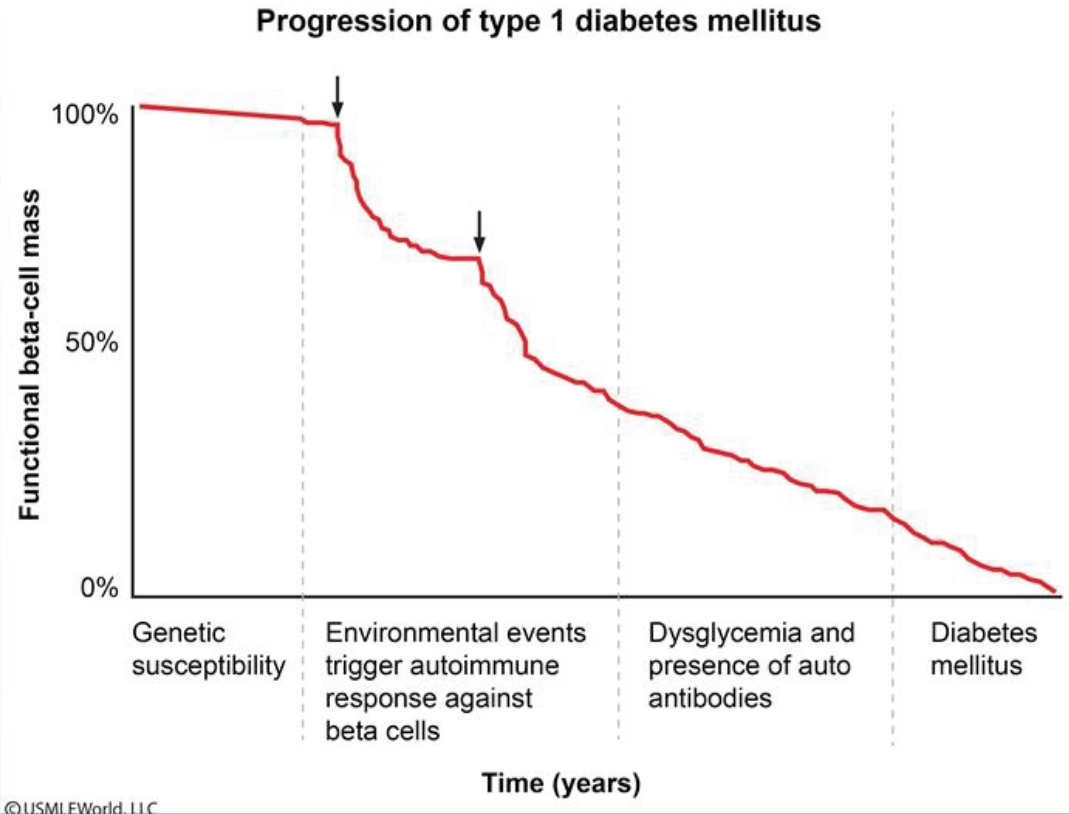
A. Abdominal fat distribution (1%)
B. Excessive body weight (2%)
C. Genetic defects in insulin secretion (19%)
D. Islet amyloid deposition (5%)
✓ E. Islet leukocytic infiltration (71%)

Correct
71% Answered correctly
48 secs Time Spent
02/06/2021 Last Updated

Explanation

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This patient is presenting with diabetic ketoacidosis, a condition that most commonly affects patients with **type 1 diabetes mellitus** due to their absolute insulin deficiency. Type 1 diabetes mellitus occurs in genetically susceptible individuals who are exposed to triggering environmental factors (eg, viral infections, environmental toxins, dietary components). This results in an **autoimmune response** against **pancreatic beta cells** that leads to progressive loss of beta cell mass. Overt manifestations of diabetes mellitus tend to develop once >90% of beta cells are destroyed. Although antibodies against islet antigens are detected in a large number of patients, they are thought to play a permissive role in disease pathogenesis; the destruction of beta cells occurs primarily through **cell-mediated immunity**. Infiltration of islets by inflammatory cells is called **insulitis** and is more prominent during the early stages of disease.

(Choices A and B) Abdominal fat deposition and excessive body weight are important contributors to insulin resistance and development of type 2 diabetes mellitus. Intra-abdominal visceral fat is more strongly related to insulin resistance than is subcutaneous fat.

(Choice C) Maturity-onset diabetes of the young is an autosomal dominant disease caused by mutations that impair glucose sensing and insulin secretion by pancreatic beta cells. It presents as non-insulin-dependent diabetes at a young age (<25) and accounts for <5% of all cases of diabetes mellitus.

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strongly related to insulin resistance than is subcutaneous fat.

(Choice C) Maturity-onset diabetes of the young is an autosomal dominant disease caused by mutations that impair glucose sensing and insulin secretion by pancreatic beta cells. It presents as non-insulin-dependent diabetes at a young age (<25) and accounts for <5% of all cases of diabetes mellitus.

(Choice D) Islet amyloid polypeptide is secreted along with insulin from pancreatic beta cells. Amyloid deposition occurs in the islets of patients with type 2 diabetes mellitus, although its role as a causative agent of beta cell dysfunction remains unknown. Patients with type 1 diabetes mellitus have low circulating levels of islet amyloid polypeptide due to extensive beta cell destruction.

Educational objective:
Autoimmune insulitis with progressive beta cell loss is the most common cause of type 1 diabetes mellitus. Insulin resistance accompanied by relative insulin deficiency is the main cause of type 2 diabetes mellitus.

References

- Advances in the cellular immunological pathogenesis of type 1 diabetes.

Pathology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early development until age 5 months. The boy subsequently developed a gradual regression of developmental milestones such as the inability to sit with support, poor head control, and loss of a social smile. His weight and height are below the fifth percentile. On physical examination, he has an enlarged liver and spleen, diminished deep tendon reflexes in all limbs, and hypotonia. Funduscopic findings are shown in the exhibit. This patient most likely has pathologic accumulation of which substrate?

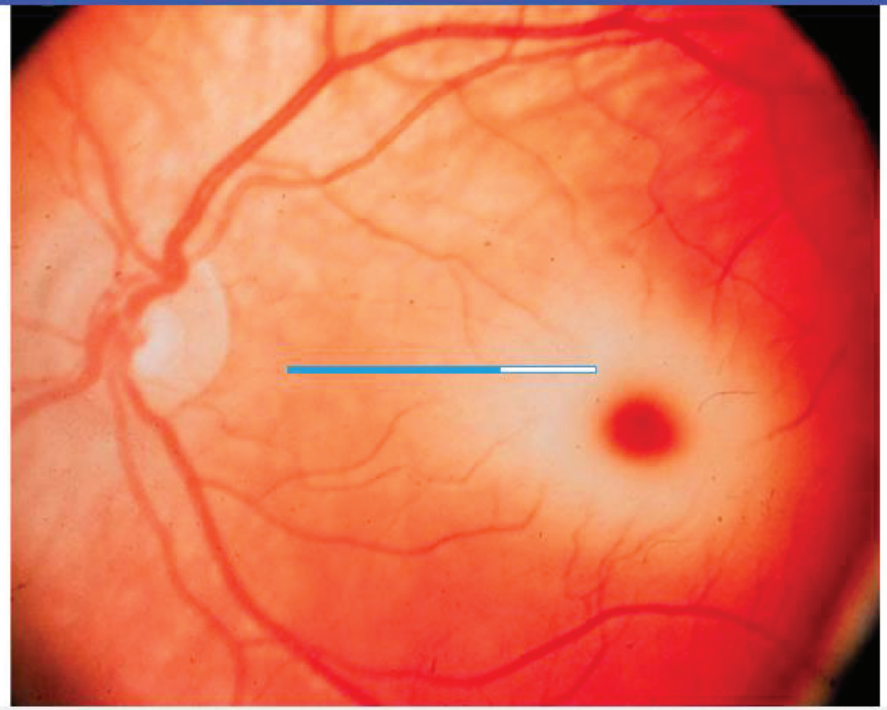
A. Cerebroside sulfate
B. Galactocerebroside
C. Globotriaosylceramide
D. Glucocerebroside
E. GM2 ganglioside
F. Sphingomyelin

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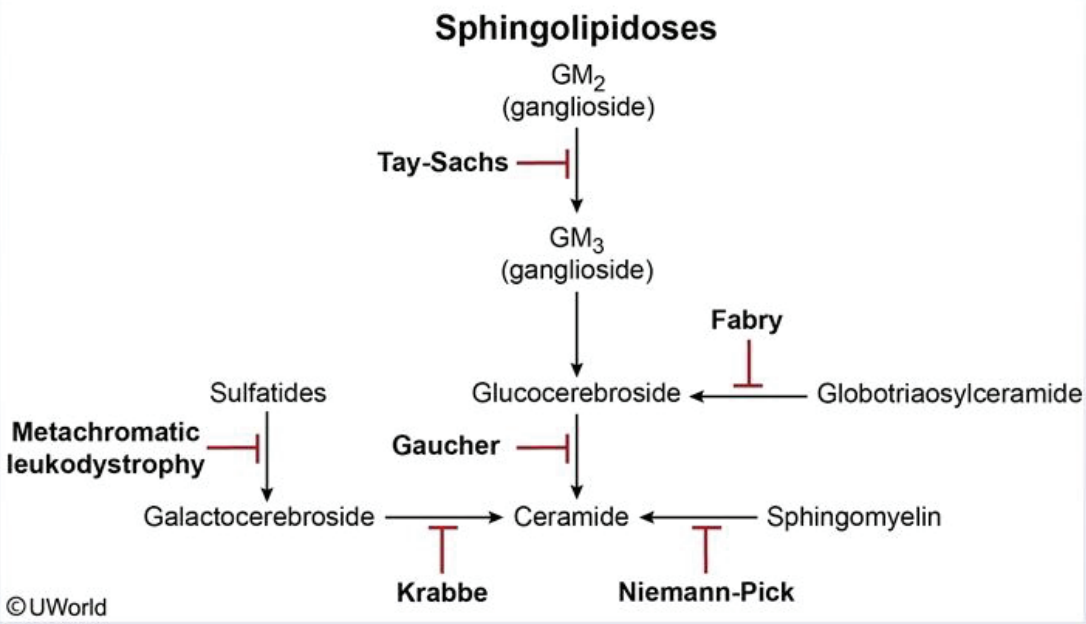
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An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early development until age 5 months. The boy subsequently developed a gradual regression of developmental milestones such as the inability to sit with support, poor head control, and loss of a social smile. His weight and height are below the fifth percentile. On physical examination, he has an enlarged liver and spleen, diminished deep tendon reflexes in all limbs, and hypotonia. Funduscopic findings are shown in the exhibit. This patient most likely has pathologic accumulation of which substrate?

A. Cerebroside sulfate (1%)
B. Galactocerebroside (11%)
C. Globotriaosylceramide (0%)
D. Glucocerebroside (8%)
E. GM2 ganglioside (17%)
F. Sphingomyelin (60%)

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Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews that is caused by **sphingomyelinase deficiency**. Sphingomyelinase is responsible for the breakdown of sphingomyelin, a lipid constituent of cell membranes. In Niemann-Pick disease, **sphingomyelin**

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Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews that is caused by **sphingomyelinase deficiency**. Sphingomyelinase is responsible for the breakdown of sphingomyelin, a lipid constituent of cell membranes. In Niemann-Pick disease, **sphingomyelin accumulation** within lysosomes results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells accumulate in the liver and spleen and cause **hepatosplenomegaly**. Progressive neuronal accumulation is responsible for **hypotonia** and **neurologic degeneration** (eg, failure to progress developmentally, loss of milestones). Retinal accumulation leads to a cherry-red macular spot. This patient presents with the classic infantile type A variant that results in hepatosplenomegaly, progressive neurologic deterioration, and death by age 3 years.

(Choice A) In patients with metachromatic leukodystrophy, central nervous system accumulation of cerebroside sulfate is caused by arylsulfatase A deficiency. Central and peripheral demyelination leads to peripheral neuropathy and ataxia.

(Choice B) In Krabbe disease, galactocerebrosidase deficiency causes accumulation of galactocerebroside and psychosine. Infants have developmental delay or regression, axial hypotonia, limb spasticity, optic atrophy, and seizures.

(Choice C) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide

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(Choice B) In Krabbe disease, galactocerebrosidase deficiency causes accumulation of galactocerebroside and psychosine. Infants have developmental delay or regression, axial hypotonia, limb spasticity, optic atrophy, and seizures.

(Choice C) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Clinical manifestations begin in childhood with neuropathic pain and dermatologic pathology (eg, telangiectasias, angiokeratomas).

(Choice D) Glucocerebroside accumulation occurs in Gaucher disease, an autosomal recessive disorder of β-glucocerebrosidase deficiency. Patients typically have hepatosplenomegaly, pancytopenia, and skeletal problems.

(Choice E) Patients with Tay-Sachs disease are deficient in β-hexosaminidase A, which leads to GM2 accumulation in neurons. Neurologic regression and cherry-red macular spots are classic symptoms (similar to Niemann-Pick disease), but hepatosplenomegaly is absent.

Educational objective:
In Niemann-Pick disease, sphingomyelinase deficiency causes accumulation of the lipid sphingomyelin. Clinical features include hepatosplenomegaly, neurologic regression, and a cherry-red macular spot in infancy.

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A 65-year-old man comes to the physician because of a non-healing ulcer on his right foot. His past medical history is significant for recurrent high blood glucose readings for the last several years, because he has failed to comply with appropriate treatment. His BMI is 37 kg/m^2. Physical examination is significant for a bilateral symmetric decrease in vibration sensation over the feet and ankles. Which of the following is most likely to be associated with this patient's condition?

A. Pancreatic islet infiltration with leukocytes
B. Pancreatic islet amyloid deposition
C. Circulating anti-islet antibodies
D. Strong linkage with HLA class II gene makeup
E. Episodic ketoacidosis that requires insulin therapy

Submit

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A 65-year-old man comes to the physician because of a non-healing ulcer on his right foot. His past medical history is significant for recurrent high blood glucose readings for the last several years, because he has failed to comply with appropriate treatment. His BMI is 37 kg/m^2. Physical examination is significant for a bilateral symmetric decrease in vibration sensation over the feet and ankles. Which of the following is most likely to be associated with this patient's condition?

A. Pancreatic islet infiltration with leukocytes (4%)
✓ B. Pancreatic islet amyloid deposition (67%)
C. Circulating anti-islet antibodies (3%)
D. Strong linkage with HLA class II gene makeup (16%)
E. Episodic ketoacidosis that requires insulin therapy (7%)

Correct
67% Answered correctly
49 secs Time Spent
11/01/2020 Last Updated

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The patient described in this vignette has type 2 diabetes mellitus (advanced age, obesity, prolonged non-compliance with treatment without immediate life-threatening consequences). The two cardinal defects involved in the pathophysiology of type 2 diabetes mellitus are increased insulin resistance and defective insulin secretion. Although still controversial, many researchers believe that increased insulin resistance is the primary abnormality in type 2 diabetes mellitus. Early in the pathogenesis of type 2 diabetes, glucose tolerance is thought to remain normal because of a compensatory increase in insulin secretion from beta cells. This compensatory insulin response by beta cells ultimately fails, causing poor glucose tolerance. A number of genetic and acquired factors are implicated in the beta-cell dysregulation of type 2 diabetes. Islet amyloid polypeptide (amylin) is one factor thought to be responsible for this beta cell dysfunction. Amylin is stored in insulin secretory granules and is co-secreted with insulin from pancreatic beta cells. Deposits of amylin are universally seen in the pancreatic islets of patients with type 2 diabetes mellitus. Amylin may play a causative role in beta cell apoptosis and defective insulin secretion; however, this theory is still controversial.

Type 1 and type 2 diabetes mellitus have very strong genetic components. Twin studies have shown a concordance rate of 50% in identical twins for diabetes mellitus type 1, and around 80% for diabetes mellitus type 2. The genes involved in the pathogenesis of diabetes mellitus type 2 remain largely

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Type 1 and type 2 diabetes mellitus have very strong genetic components. Twin studies have shown a concordance rate of 50% in identical twins for diabetes mellitus type 1, and around 80% for diabetes mellitus type 2. The genes involved in the pathogenesis of diabetes mellitus type 2 remain largely unknown. Gene polymorphism within the major histocompatibility complex contributes to type 1 diabetes mellitus disease in humans. HLA-DQ and -DR are the most important determinants of type 1 diabetes mellitus. In the general population, DR3 and DR4 are seen in approximately 40% of subjects; however, in patients with type 1 diabetes mellitus, DR3 and DR4 haplotypes are seen in more than 90% of subjects.

(Choices A, C, D & E) These are features of type 1 diabetes mellitus. Type 1 diabetes occurs when an autoimmune response is triggered by an environmental insult in genetically susceptible individuals. Patients with type 2 diabetes retain at least some beta cell function, but patients with type 1 diabetes mellitus develop absolute deficiency of insulin secondary to immune destruction of pancreatic beta cells. These patients need insulin for survival. Discontinuation of insulin treatment results in ketoacidosis.

Educational objective:

Pancreatic islet amyloid deposition is characteristic of type 2 diabetes mellitus. A strong linkage with HLA class II gene makeup, pancreatic islet infiltration with leukocytes (insulitis), and antibodies against islet antigens are frequently seen in type 1 diabetes.

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A 37-year-old woman comes to the office due to a two-month history of abdominal pain, salt craving, and weight loss. She also has dizziness on standing. The patient has no chronic medical conditions and takes no medications. She does not use tobacco, alcohol, or illicit drugs. Her mother and sister have hypothyroidism. Blood pressure is 100/70 mm Hg supine and 80/50 mm Hg standing. Laboratory results are as follows:

Sodium	129 mEq/L
Potassium	5.9 mEq/L
Chloride	100 mEq/L
Bicarbonate	21 mEq/L
Creatinine	1.4 mg/dL
Blood urea nitrogen	38 mg/dL

Which of the following changes in circulating hormone levels are expected in this patient?

	Cortisol	Aldosterone	Antidiuretic	Norepinephrine

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Bicarbonate	21 mEq/L
Creatinine	1.4 mg/dL
Blood urea nitrogen	38 mg/dL

Which of the following changes in circulating hormone levels are expected in this patient?

	Cortisol	Aldosterone	Antidiuretic hormone	Norepinephrine
A.	↓	↓	↑	↑
B.	Normal	Normal	↑	Normal
C.	Normal	↑	↑	↑
D.	↓	↑	↑	↑
E.	↑	↑	↑	↑
F.	↑	↓	↓	↓

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Blood urea nitrogen 38 mg/dL

Which of the following changes in circulating hormone levels are expected in this patient?

		Cortisol	Aldosterone	Antidiuretic hormone	Norepinephrine	
✓	A.	↓	↓	↑	↑	(66%)
	B.	~~Normal~~	~~Normal~~	↕	~~Normal~~	(2%)
	C.	~~Normal~~	↕	↕	↕	(5%)
	D.	↓	↕	↕	↕	(6%)
	E.	↕	↕	↕	↕	(7%)
	F.	↑	↓	↓	↓	(12%)

Correct

66%
Answered correctly

02 mins, 31 secs
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12/07/2020
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This patient has multiple signs and symptoms of **primary adrenal insufficiency** (PAI) (also known as Addison disease), including abdominal pain, weight loss, salt craving, orthostasis (dizziness on standing), and electrolyte disturbance. PAI usually results from autoimmune destruction of the bilateral adrenal cortex and is more likely to occur in patients with a personal or family **history of autoimmune disease** (eg, Hashimoto thyroiditis). Because all 3 layers of the adrenal cortex are affected, clinical manifestations result from a reduction in circulating mineralocorticoids, glucocorticoids, and androgens.

Reduced aldosterone, the principal mineralocorticoid in the body, leads to markedly decreased sodium absorption by the renal collecting tubule principal cells with consequent retention of potassium (leading to **hyperkalemia**). The decrease in total body sodium results in **hypovolemia** and **hypotension** that may lead to renal insufficiency. The hypovolemia provides nonosmotic stimulus for **antidiuretic hormone (ADH) secretion**, which stimulates water retention and leads to **hyponatremia**.

Cortisol, the main glucocorticoid in the body, normally inhibits ADH secretion; therefore, **reduced cortisol** further contributes to hyponatremia. Cortisol is also necessary for the synthesis of epinephrine in the adrenal medulla; the consequent reduction in circulating epinephrine leads to a compensatory **increase in norepinephrine** to increase vascular tone in an effort to maintain blood pressure.

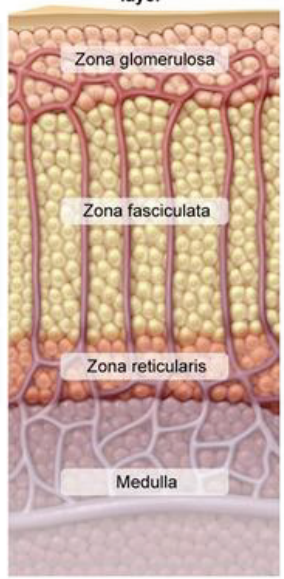
(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the

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Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		



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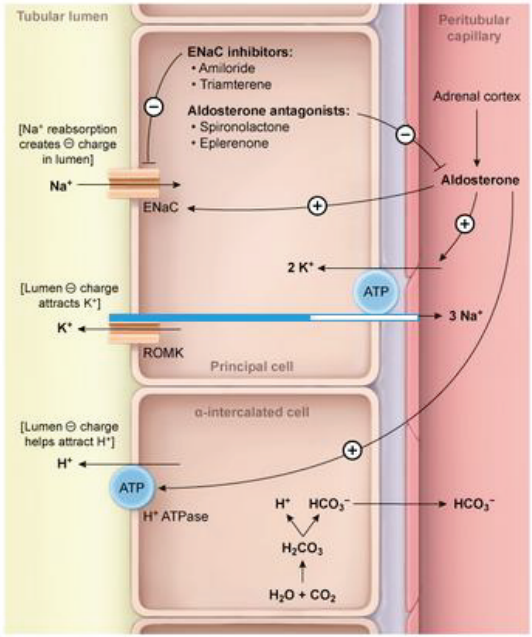
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(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the

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Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the

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(Choice B) Increased ADH and normal levels of cortisol, aldosterone, and norepinephrine occur in the syndrome of inappropriate ADH secretion (SIADH). SIADH presents with hyponatremia, but it does not explain this patient's hyperkalemia, salt craving, and orthostatic symptoms.

(Choices C, D, and E) Elevations in aldosterone, ADH, and norepinephrine occur in conditions that decrease effective arterial blood volume and renal perfusion (eg, heart failure, cirrhosis, dehydration). Cortisol levels are often elevated in dehydration and heart failure; total cortisol is low in cirrhosis due to reduced cortisol-binding protein levels.

(Choice F) Increased cortisol with reduced levels of aldosterone, ADH, and norepinephrine can occur with ectopic ACTH production (eg, due to small cell lung cancer). Aldosterone synthesis is mostly independent of ACTH and is suppressed because cortisol and other glucocorticoids have some mineralocorticoid activity. Levels of ADH and norepinephrine are also generally suppressed.

Educational objective:
Primary adrenal insufficiency usually involves autoimmune destruction of the bilateral adrenal cortex. Reduced aldosterone production leads to renal salt wasting with hypovolemia, hypotension, and hyperkalemia. The hypovolemia and reduced cortisol-induced inhibition of antidiuretic hormone lead to water retention and hyponatremia. Reduced cortisol also causes decreased circulating epinephrine with a

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explain this patient's hyperkalemia, salt craving, and orthostatic symptoms.

(Choices C, D, and E) Elevations in aldosterone, ADH, and norepinephrine occur in conditions that decrease effective arterial blood volume and renal perfusion (eg, heart failure, cirrhosis, dehydration). Cortisol levels are often elevated in dehydration and heart failure; total cortisol is low in cirrhosis due to reduced cortisol-binding protein levels.

(Choice F) Increased cortisol with reduced levels of aldosterone, ADH, and norepinephrine can occur with ectopic ACTH production (eg, due to small cell lung cancer). Aldosterone synthesis is mostly independent of ACTH and is suppressed because cortisol and other glucocorticoids have some mineralocorticoid activity. Levels of ADH and norepinephrine are also generally suppressed.

Educational objective:
Primary adrenal insufficiency usually involves autoimmune destruction of the bilateral adrenal cortex. Reduced aldosterone production leads to renal salt wasting with hypovolemia, hypotension, and hyperkalemia. The hypovolemia and reduced cortisol-induced inhibition of antidiuretic hormone lead to water retention and hyponatremia. Reduced cortisol also causes decreased circulating epinephrine with a compensatory increase in norepinephrine.

Pathology Endocrine, Diabetes & Metabolism Adrenal insufficiency

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A 45-year-old man comes to the emergency department after experiencing sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

A. Defective central thirst regulation
B. Impaired renal concentrating ability
C. Inadequate dietary sodium intake
D. Increased antidiuretic hormone secretion
E. Stress-induced excessive cortisol levels

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A 45-year-old man comes to the emergency department after experiencing sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

- A. ~~Defective central thirst regulation~~ (19%)
- B. ~~Impaired renal concentrating ability~~ (9%)
- C. ~~Inadequate dietary sodium intake~~ (1%)
- ✓ D. Increased antidiuretic hormone secretion (63%)
- E. Stress-induced excessive cortisol levels (6%)

Correct

63% Answered correctly

02 mins, 50 secs Time Spent

08/23/2020 Last Updated

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Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)

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Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Low serum osmolality • High urine osmolality • High urine sodium

ADH = antidiuretic hormone; **JVD** = jugular venous distension; **NSAIDs** =

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This patient likely has the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH), the most common cause of **hyponatremia** following subarachnoid hemorrhage (SAH). Antidiuretic hormone (ADH) is normally released by the hypothalamus and posterior pituitary in response to elevated serum osmolality (eg, following water deprivation) or decreased arterial blood volume. ADH promotes renal water reabsorption, which leads to concentration of the urine, extracellular fluid volume expansion, and lowering of serum osmolality and serum sodium. Hypothalamic damage following SAH is thought to trigger **excessive production of ADH**, resulting in the classic SIADH features of **hypotonicity** (ie, low serum osmolarity), **hyponatremia**, and persistently concentrated urine (ie, **high urine osmolality**).

In addition to SIADH, hyponatremia after SAH can also be due to cerebral salt wasting (caused by increased secretion of brain natriuretic peptide, which leads to urinary sodium losses) or acute cortisol deficiency (eg, from pituitary injury, leading to hypotension) **(Choice E)**. In both conditions, decreased extracellular fluid volume causes a secondary increase in ADH and worsening hyponatremia.

(Choice A) In primary polydipsia, defective central thirst regulation leads to excessive water intake and hyponatremia. ADH levels are low, rather than high. Primary polydipsia is typically seen with certain psychiatric conditions (eg, schizophrenia) or use of psychotropic medications. It is not commonly associated with SAH.

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associated with SAH.

(Choice B) Impaired renal concentrating ability is seen in diabetes insipidus (DI), which occurs either due to ADH resistance (in nephrogenic DI) or decreased ADH production (in central DI). DI may follow cerebral injury; however, it does not cause hyponatremia. Rather, DI results in a clinical picture opposite that of SIADH, featuring hypernatremia, increased serum osmolality, and dilute urine (ie, low urine osmolality).

(Choice C) Inadequate dietary intake of sodium is a rare cause of hyponatremia primarily seen in cases of chronic alcohol abuse (eg, beer potomania). SIADH is a more likely cause of hyponatremia in this patient.

Educational objective:
Hyponatremia following cerebral injury (eg, subarachnoid hemorrhage) is commonly due to the syndrome of inappropriate antidiuretic hormone secretion. Injury to the hypothalamus leads to increased secretion of antidiuretic hormone, which in turn leads to water retention, low serum osmolality, and increased urinary sodium excretion.

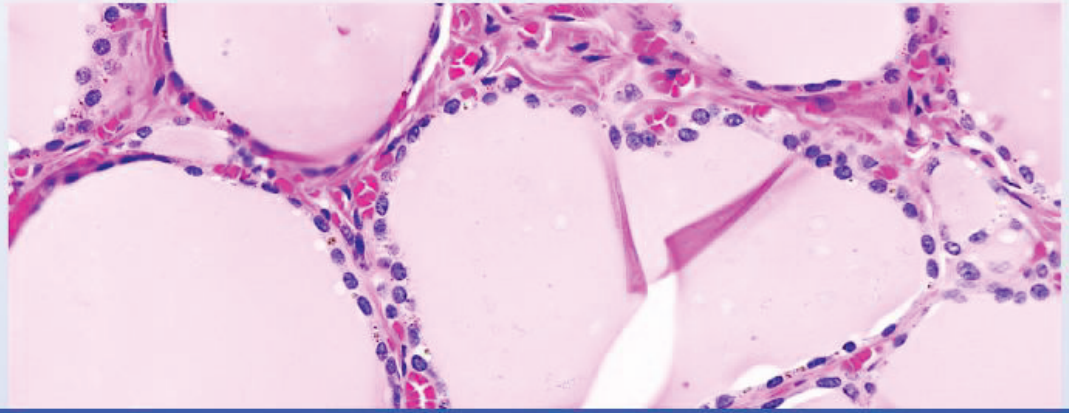
References

- Diagnosis and management of subarachnoid hemorrhage.
- Hyponatremia after spontaneous aneurysmal subarachnoid hemorrhage – a prospective observational study

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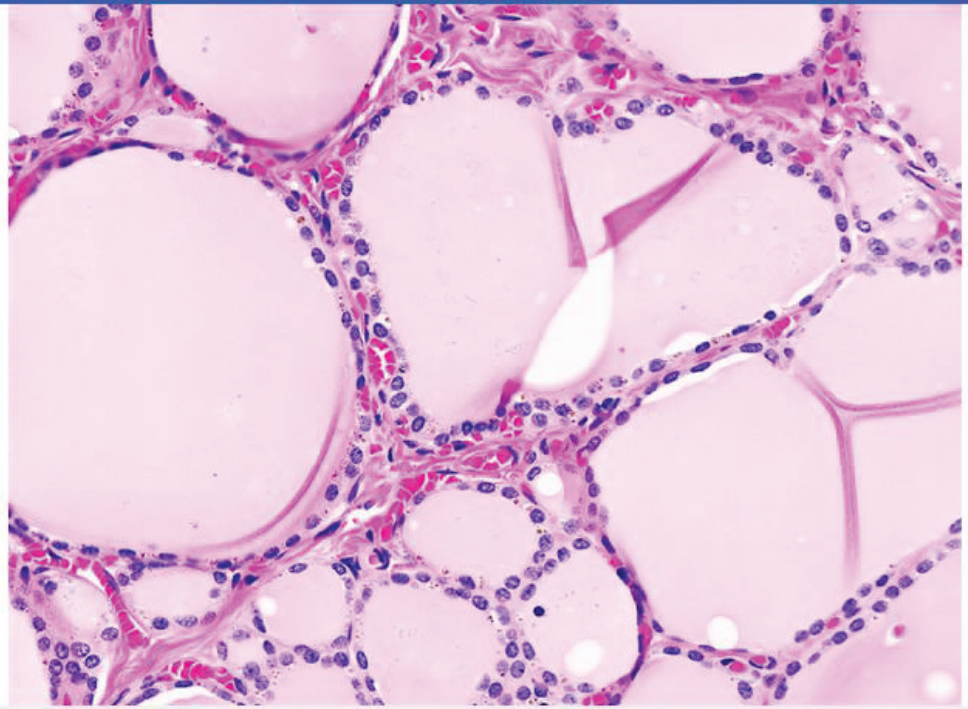
A 13-year-old boy is brought to the clinic due to progressive difficulty with breathing, hoarseness, and dysphagia. The symptoms began insidiously 6 months ago but have rapidly become worse in the last 4 weeks. The patient has no associated skin rash, pharyngeal pain, fever, weight loss, or loss of appetite. Medical history is unremarkable and the patient takes no medications. He is up to date on scheduled vaccinations. The patient's parents and siblings have no history of significant health problems. Vital signs are normal, and he is at 70th percentile for height and weight. Oropharyngeal examination reveals a large, red lingual mass. The patient subsequently undergoes excision of the mass; histopathologic preparation of the recovered tissue is shown in the image below.



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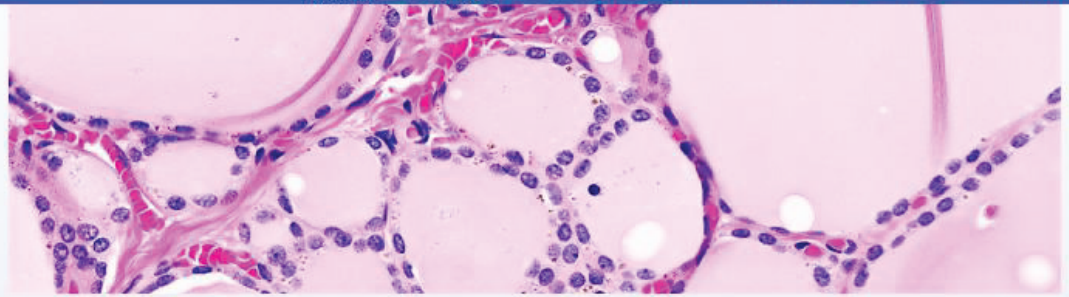
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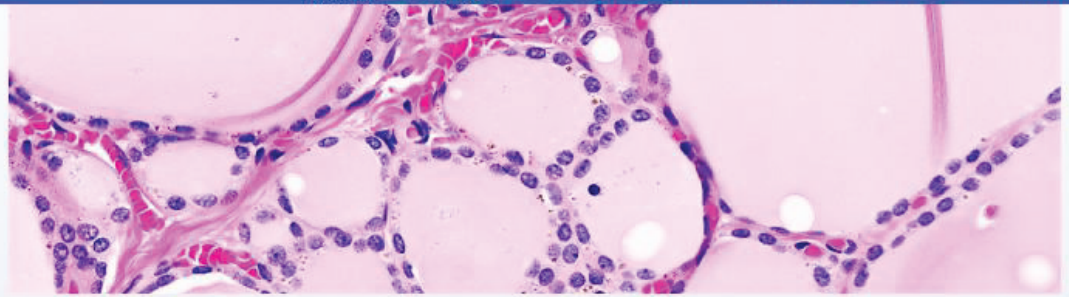


Failure of which of the following embryologic processes is most likely responsible for this patient's lesion?

- A. Apoptosis
- B. Differentiation
- C. Fusion
- D. Migration
- E. Proliferation

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Failure of which of the following embryologic processes is most likely responsible for this patient's lesion?

- A. Apoptosis (14%)
- B. Differentiation (3%)
- C. Fusion (2%)
- ✓ D. Migration (76%)
- E. Proliferation (3%)

Correct

76%

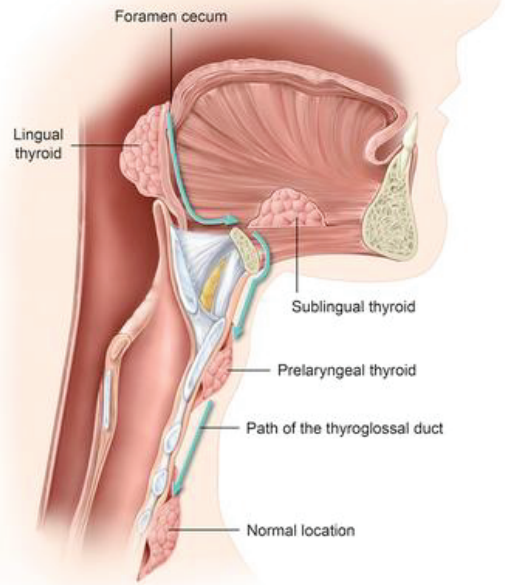
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Thyroid migration



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This patient's pathologic specimen shows normal thyroid follicles containing colloid, consistent with a **lingual thyroid**. The thyroid gland is formed from an outpouching (evagination) of the pharyngeal epithelium and subsequently descends to the lower neck anterior to the upper trachea and larynx. The lowest part of the evagination forms the thyroid gland and the remaining portion forms the **thyroglossal duct**, which extends from the foramen cecum on the dorsal surface of the tongue to the superior border of the thyroid isthmus.

Due to **failure of migration**, the thyroid can reside anywhere along the thyroglossal duct's usual path, including the tongue (lingual thyroid). Enlargement of a lingual thyroid can lead to **obstructive symptoms** (eg, dysphagia, dysphonia, dyspnea), typically during times of heightened thyroid stimulation (eg, puberty, pregnancy). Sometimes, this lingual thyroid is the only thyroid tissue in the body, so hypothyroidism can occur if it is removed.

(Choice A) Apoptosis is the process of programmed cell death and is important in regulating the turnover of cells. Failure of apoptosis during fetal development can result in conditions such as duodenal atresia and syndactyly (ie, fusion of adjacent digits).

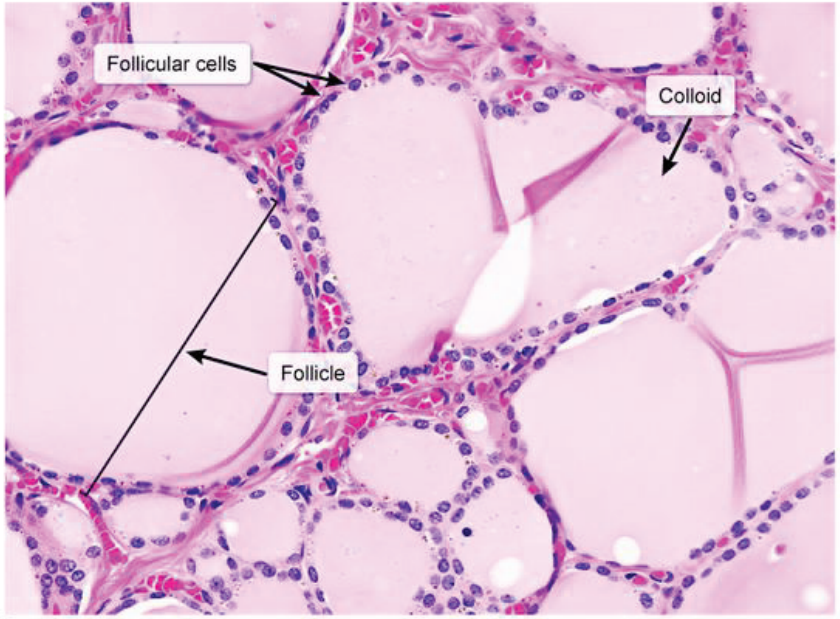
(Choice B) Differentiation is the formation of mature cells from undifferentiated precursor cells (eg,

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Normal thyroid gland



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(Choice B) Differentiation is the formation of mature cells from undifferentiated precursor cells (eg,

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(Choice B) Differentiation is the formation of mature cells from undifferentiated precursor cells (eg, formation of red blood cells, white blood cells, and platelets from bone marrow stem cells). Although thyroid cells do differentiate after their descent from the pharynx, defective differentiation would result in impaired thyroid follicle formation.

(Choice C) Fusion is the joining of two opposing tissues to form one continuous structure. Disruption of this process leads to a variety of birth defects, including cleft palate, atrioventricular septal defects, pancreatic divisum, and neural tube defects.

(Choice E) Proliferation denotes an increase in the number of cells via mitosis. Failure of proliferation during fetal development can result in organ hypoplasia (eg, thymus abnormalities in DiGeorge syndrome).

Educational objective:

The thyroid gland is formed from evagination of the pharyngeal epithelium and descends to the lower neck. Due to failure of migration, the thyroid can reside anywhere along the thyroglossal duct's usual path, including the tongue (lingual thyroid).

References

- Morphological, diagnostic and surgical features of ectopic thyroid gland: a review of literature.

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A 34-year-old woman comes to the office due to inability to lose weight despite diet and exercise. She reports that she gained a significant amount of weight after she stopped smoking 4 years ago. The patient has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

A. Delayed gastric emptying
B. Lipase inhibition
C. Opioid antagonist
D. Reduced presynaptic reuptake of serotonin
E. Release of norepinephrine

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has tried several commercial weight-loss diet programs in the last year without success. She wants to lose at least 4.5 kg (10 lb) over the next few months before she gets married. The patient does not have any other medical conditions and takes no medications. Blood pressure is 122/80 mm Hg and pulse is 78/min. BMI is 33 kg/m^2. Physical examination shows an obese habitus but is otherwise unremarkable. Laboratory testing for secondary causes of weight gain is unrevealing. In addition to encouraging continued efforts at lifestyle change, the physician prescribes a short course of oral phentermine for weight loss. The weight loss induced by this medication is caused by which of the following mechanisms?

A. Delayed gastric emptying (32%)
B. Lipase inhibition (10%)
C. Opioid antagonist (3%)
D. Reduced presynaptic reuptake of serotonin (6%)
✓ E. Release of norepinephrine (46%)

Correct

46%
Answered correctly

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Time Spent

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Explanation

Medications for weight loss		
	Mechanism of action	**Notable features**
Sympathomimetic amines (ie, phentermine, diethylpropion, benzphetamine)	Stimulant/CAS	• High rate of weight regain • Not recommended for patients with CVD
Orlistat	Intestinal lipase inhibitor	• Significant gastrointestinal side effects
Bupropion/naltrexone	CAS (antidepressant + opioid antagonist)	• Lowers seizure threshold • May also assist in smoking cessation

CAS = central appetite suppressant; **CVD** = cardiovascular disease.

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated

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CAS = central appetite suppressant; **CVD** = cardiovascular disease.

Norepinephrine-releasing agents (eg, **phentermine**) are sympathomimetic weight-loss drugs indicated for **short-term** (≤12 weeks) treatment of obesity. They work by stimulating release and inhibiting reuptake of norepinephrine and, to a lesser extent, serotonin and dopamine. Subjective effects include an **increased** sensation of **satiety** and subsequently reduced caloric intake.

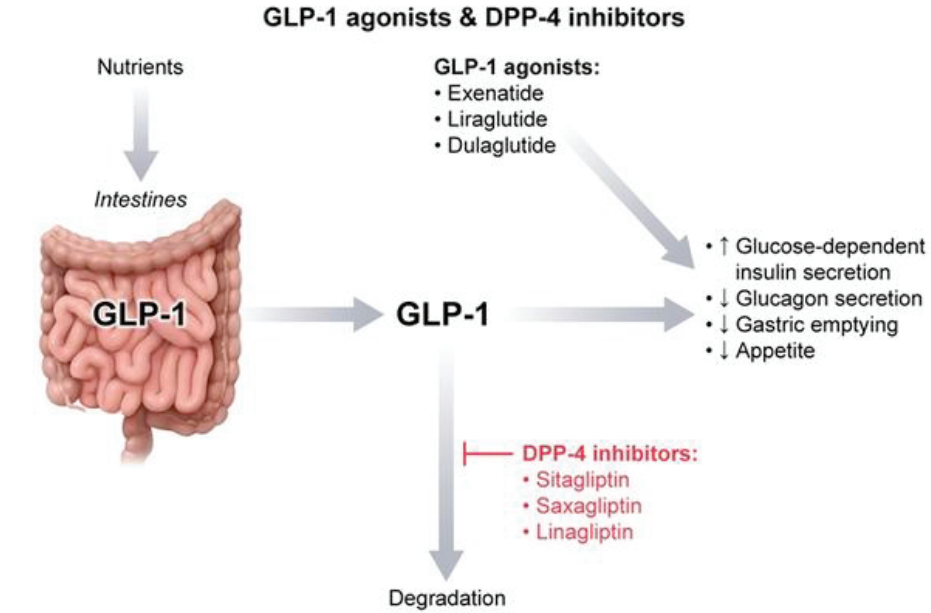
Because of the increased sympathetic activity associated with these drugs, they can raise blood pressure and should be **avoided** in patients with comorbid **hypertension** or **heart disease**. Norepinephrine-releasing agents can induce brisk initial weight loss but are notable for poor long-term benefit, and most patients regain the lost weight following discontinuation.

(Choice A) Glucagonlike peptide-1 (GLP-1) agonists (eg, liraglutide) increase glucose-dependent insulin secretion and are most commonly used in treatment of type 2 diabetes mellitus. In addition, GLP-1 agonists cause delayed gastric emptying and decreased appetite, leading to weight loss.

(Choice B) Orlistat is an intestinal lipase inhibitor. It acts by reducing the digestion and subsequent absorption of dietary fats. The increased residual fat content in the intestinal lumen can lead to intestinal discomfort, diarrhea, fecal incontinence, and impaired absorption of fat-soluble vitamins (eg, vitamin D).

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absorption of dietary fats. The increased residual fat content in the intestinal lumen can lead to intestinal discomfort, diarrhea, fecal incontinence, and impaired absorption of fat-soluble vitamins (eg, vitamin D).

(Choice C) Naltrexone is an opioid antagonist indicated for the treatment of opioid abuse and alcohol dependence. It is also used in a combination pill with bupropion for weight loss, in which it is thought to potentiate the otherwise minor weight-loss effects of bupropion.

(Choice D) In addition to treating depression and anxiety, selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine) are commonly used in the treatment of eating disorders, especially bulimia nervosa. Although some patients taking SSRIs experience minor weight loss, the effects on weight are variable, and these medications are not prescribed for weight loss.

Educational objective:

Norepinephrine-releasing agents (eg, phentermine) are sympathomimetic weight-loss drugs indicated for short-term treatment of obesity. They stimulate the release and inhibit the reuptake of norepinephrine. Subjective effects include an increased sensation of satiety, leading to reduced caloric intake. Weight regain after cessation is common with these drugs.

References

- Obesity pharmacotherapy.

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A 15-year-old boy comes to the office for evaluation of a neck mass. The patient first noticed the mass a month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

A. Adrenal cortex
B. Adrenal medulla
C. Anterior pituitary
D. Pancreatic islets
E. Thymus

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month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

- A. Adrenal cortex (3%)
- ✓ B. Adrenal medulla (82%)
- C. Anterior pituitary (5%)
- D. Pancreatic islets (6%)
- E. Thymus (1%)

Correct

82%

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Explanation

Multiple endocrine neoplasia type 2	
Inheritance	• Autosomal dominant • Germ-line activating mutations of *RET* proto-oncogene
Type 2A	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Parathyroid hyperplasia
Type 2B	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Mucosal neuromas, marfanoid habitus

This patient has **medullary thyroid cancer** (MTC), a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells. Most cases of MTC are sporadic, but approximately 20% are familial, due to germline mutations of the ***RET* proto-oncogene**. Multiple endocrine neoplasia type 2

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This patient has **medullary thyroid cancer** (MTC), a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells. Most cases of MTC are sporadic, but approximately 20% are familial, due to germline mutations of the ***RET* proto-oncogene**. Multiple endocrine neoplasia type 2 (**MEN2**) is the most common inherited disorder associated with activating *RET* mutations, and is characterized by:

- MTC
- Pheochromocytoma
- Parathyroid hyperplasia (type 2A) or marfanoid habitus (tall, slender build, increased limb to height ratio) and mucosal neuromas (type 2B)

Pheochromocytoma is a catecholamine-secreting neoplasm arising from the chromaffin cells of the **adrenal medulla**. Up to 50% of patients with MEN2 develop pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia can precipitate a catecholamine (epinephrine and norepinephrine) surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation. Therefore, patients who have MTC associated with germline *RET* mutations should be screened for pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

(Choices A, C, D and E) MEN1 is characterized by anterior pituitary adenomas, primary

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pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

(Choices A, C, D and E) MEN1 is characterized by anterior pituitary adenomas, primary hyperparathyroidism (due to parathyroid adenomas or hyperplasia), and neuroendocrine tumors of the pancreas and gastrointestinal tract (eg, gastrinoma, insulinoma). A number of other tumors are also more frequent in MEN1, including adrenocortical adenomas and neuroendocrine thymomas (thymic carcinoid). However, MEN1 is due to mutations in the *MEN1* gene (not *RET*) and is not associated with MTC.

Educational objective:

Multiple endocrine neoplasia type 2 is caused by germline activating mutations in the *RET* proto-oncogene and frequently results in both medullary thyroid cancer and pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia (eg, preparation for thyroidectomy) can precipitate a catecholamine surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation.

References

- The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer.

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www.ncbi.nlm.nih.gov/pubmed/20664475

Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

A. Degradation in lysosomes
B. Degradation in proteasomes
C. Degradation in the rough endoplasmic reticulum
D. Direct translocation across the plasma membrane
E. Storage in secretory granules

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A. Degradation in lysosomes (9%)

B. Degradation in proteasomes (30%)

C. Degradation in the rough endoplasmic reticulum (8%)

D. Direct translocation across the plasma membrane (13%)

E. Storage in secretory granules (39%)

Incorrect

30%

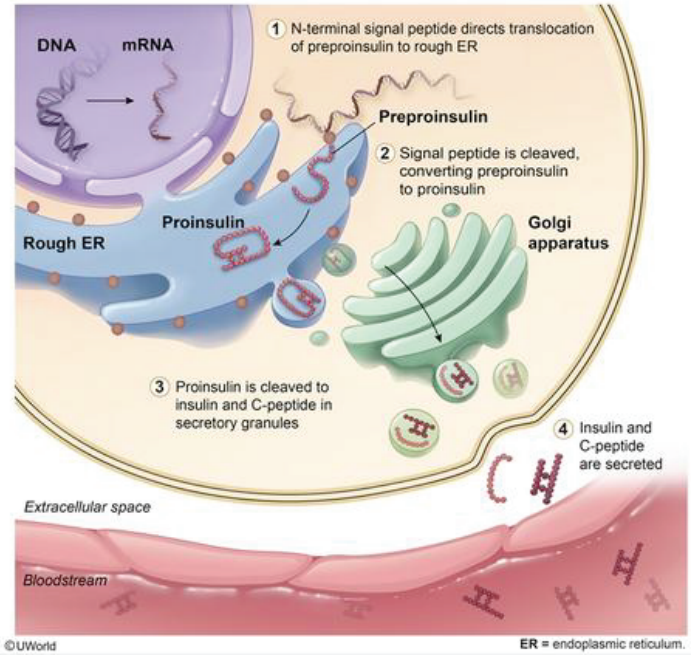
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Insulin synthesis and secretion



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Insulin, a polypeptide hormone synthesized by pancreatic beta cells, is released in response to elevated glucose levels. Insulin mRNA codes for **preproinsulin**, a larger precursor molecule that begins with a hydrophobic N-terminal signal peptide. Shortly after translation begins, this signal sequence interacts with cytosolic signal recognition peptide, which halts protein synthesis until the ribosome translocates to the rough endoplasmic reticulum (RER). Once bound to the RER, translation resumes and the growing peptide chain is extruded into the RER. The N-terminal signal peptide is then cleaved from preproinsulin to yield **proinsulin**.

Proinsulin undergoes conformational changes and the addition of 3 disulfide bonds in the RER. Proinsulin is then transported to the Golgi apparatus, where it is packed into secretory granules. Endopeptidases in the secretory granules cleave proinsulin into **insulin** and **C-peptide**, which are then stored within the granules until they are secreted from the cell via exocytosis **(Choices A, B, and C)**.

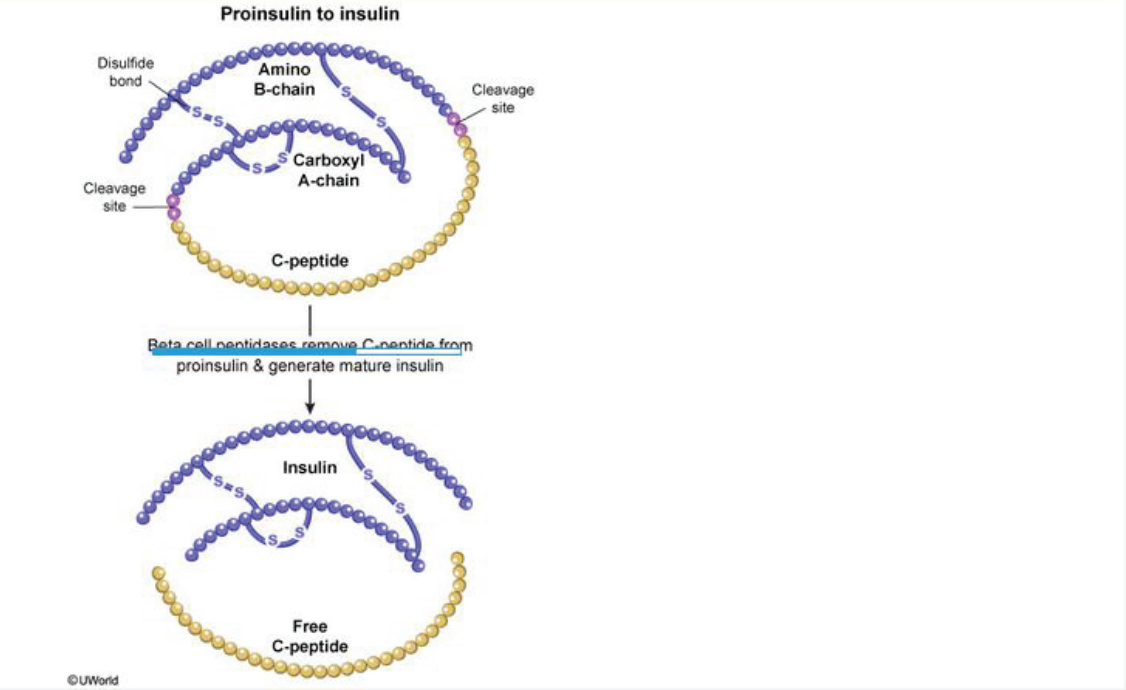
Exogenous insulin administered to patients with diabetes does not contain C-peptide. However, C-peptide released from beta cells remains in the circulation with a half-life of approximately 35 minutes and can be assayed as a surrogate marker for endogenous insulin production.

(Choice D) Most proteins destined for the extracellular space have a signaling sequence that directs them to the RER/Golgi apparatus, where they are packaged into secretory vesicles. However, a few proteins

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(Choice D) Most proteins destined for the extracellular space have a signaling sequence that directs them to the RER/Golgi apparatus, where they are packaged into secretory vesicles. However, a few proteins, such as interleukin-1, lack a signaling sequence and are secreted directly from the cytoplasm via an unconventional mechanism.

Educational objective:

Cleavage of proinsulin in pancreatic beta-cell secretory granules yields insulin and C-peptide, which are stored in the granules until they are secreted in equimolar amounts.

References

- Regulation of insulin synthesis and secretion and pancreatic beta-cell dysfunction in diabetes.

Physiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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Researchers studying the pathophysiology of diabetes mellitus identify a family with an inherited mutation in the insulin gene. The mutation results in a single amino acid substitution in the proinsulin molecule. However, affected family members are asymptomatic, and most have completely normal blood glucose levels. Analysis of the mature insulin molecule shows that it is identical to normal human insulin. The researchers conclude that the amino acid substitution affects a segment of proinsulin removed during post-translational processing of the protein. The polypeptide segment containing the mutation is most likely to undergo which of the following processes within pancreatic beta cells?

A. Degradation in lysosomes (9%)

B. Degradation in proteasomes (30%)

C. Degradation in the rough endoplasmic reticulum (8%)

D. Direct translocation across the plasma membrane (13%)

E. Storage in secretory granules (39%)

Incorrect

30%

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A 43-year-old woman comes to the office due to episodic confusion, blurred vision, tremors, and sweating. The episodes have increased in intensity in the past few months and seem to occur any time during the day. Her symptoms are relieved by drinking orange juice. During a recent episode, the patient's blood glucose level was 32 mg/dL as measured by her husband's home glucose meter. Medical history includes major depression and irritable bowel syndrome. Laboratory studies performed during the next episode of symptoms show the following results:

Glucose	35 mg/dL	
Insulin	18 µU/mL	(normal: <3 µU/mL)
C-peptide	4.01 ng/mL	(normal: <0.6ng/mL)

Which of the following is the most likely cause of this patient's symptoms?

A. Alpha cell tumor
B. Insulin administration
C. Somatostatinoma

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Which of the following is the most likely cause of this patient's symptoms?

A. Alpha cell tumor
B. Insulin administration
C. Somatostatinoma
D. Sulfonylurea use
E. VIP-secreting tumor

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Insulin	18 µU/mL	(normal: <3 µU/mL)
C-peptide	4.01 ng/mL	(normal: <0.6ng/mL)

Which of the following is the most likely cause of this patient's symptoms?

A. ~~Alpha cell tumor~~ (5%)
B. ~~Insulin administration~~ (7%)
C. Somatostatinoma (5%)
✓ D. Sulfonylurea use (72%)
E. VIP-secreting tumor (8%)

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Evaluation of hypoglycemia

	Serum insulin	C-peptide	Hypoglycemic drug assay
Exogenous insulin	Normal/increased	**Low**	Negative
Oral hypoglycemic agents	Normal/increased	Normal/elevated	**Positive**
Insulinoma	Normal/increased	Normal/elevated	Negative

This patient has symptomatic **hypoglycemia**, confirmed by the **Whipple triad**:

- Symptoms consistent with hypoglycemia (eg, tremor, diaphoresis, confusion)
- Low blood glucose level
- Relief of hypoglycemic symptoms when the blood glucose level is corrected

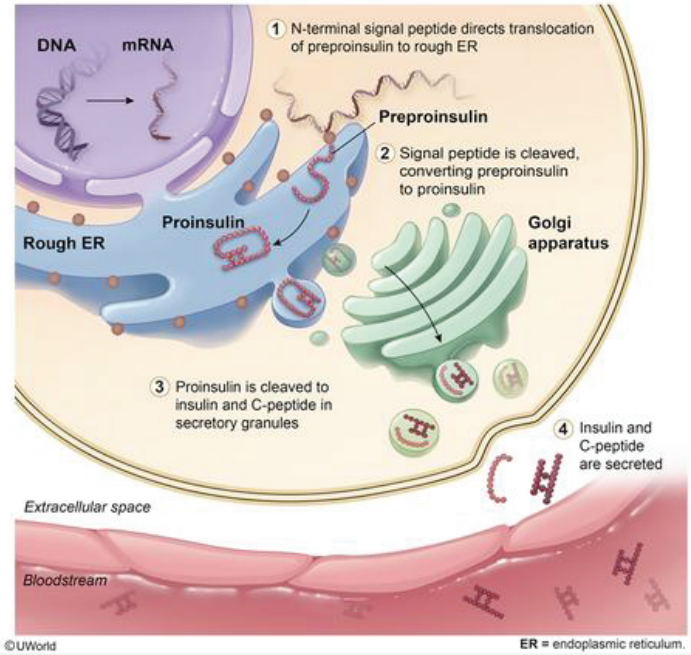
Insulin is initially synthesized as preproinsulin, after which the signal peptide is removed, yielding proinsulin. In the secretory granules, proinsulin is cleaved into **insulin** and **C-peptide**, which are then released together in equimolar amounts. Normally, as blood glucose falls, endogenous insulin secretion is suppressed, and serum levels of both insulin and C-peptide drop.

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- Relief of hypoglycemic symptoms when the blood glucose level is corrected

Exhibit Display

Insulin synthesis and secretion



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erythematous rash affecting the face, groin, and extremities).

(Choice B) Hypoglycemia due to exogenous insulin injection, which does not contain C-peptide, is associated with an elevated serum insulin level but an undetectable C-peptide level.

(Choice C) Somatostatinoma is a rare tumor of pancreatic delta cells that is associated with hyperglycemia, weight loss, abdominal pain, steatorrhea, cholelithiasis, and hypochlorhydria. These manifestations are due to somatostatin-induced inhibition of insulin, gastrin, secretin, and cholecystokinin secretion, as well as decreased gastrointestinal motility.

(Choice E) VIPomas are non–beta cell pancreatic islet cell tumors that hypersecrete vasoactive intestinal polypeptide (VIP). Features include watery diarrhea, hypokalemia, and impaired gastric acid secretion.

Educational objective:
Hypoglycemia is characterized by tremor, diaphoresis, and confusion in association with a low blood glucose level and resolution of symptoms when the blood glucose level is corrected. Hypoglycemia with elevated insulin and low C-peptide levels suggests exogenous insulin injection, whereas elevated C-peptide suggests an insulin secretagogue or insulin-secreting tumor.

References

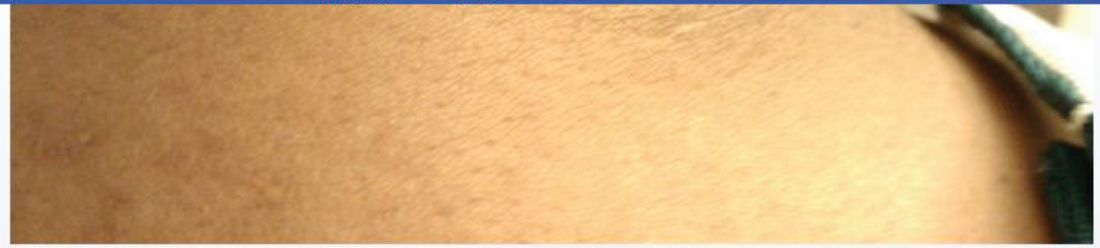
- Approach to the patient with spontaneous hypoglycemia

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A 50-year-old woman comes to the office to discuss weight gain. She has gained about 13.6 kg (30 lb) over the last 2 years, which she attributes to excessive eating and not exercising. The patient is otherwise feeling well, and her past medical history is unremarkable. However, she has a strong family history of type 2 diabetes mellitus. Blood pressure is 150/90 mm Hg and pulse is 75/min. BMI is 30.3 kg/m^2. Hyperpigmentation in skinfolds is noted at the neck as shown in the image below.



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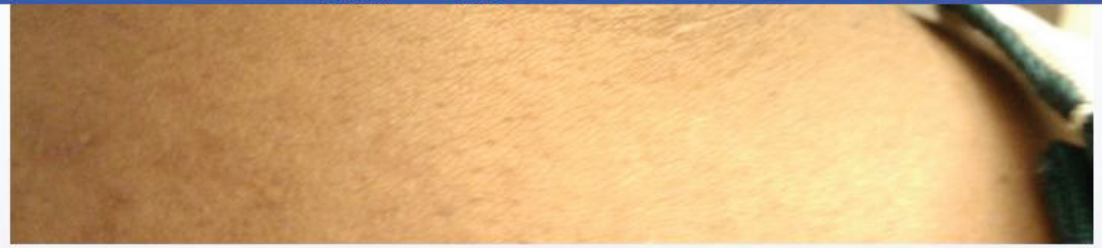


Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate
B. C-peptide
C. Free fatty acids
D. High-density lipoprotein
E. Low-density lipoprotein

Submit

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Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate (8%)
B. C-peptide (37%)
C. Free fatty acids (29%)
D. High-density lipoprotein (0%)
E. Low-density lipoprotein (23%)

Correct

29%

13 secs

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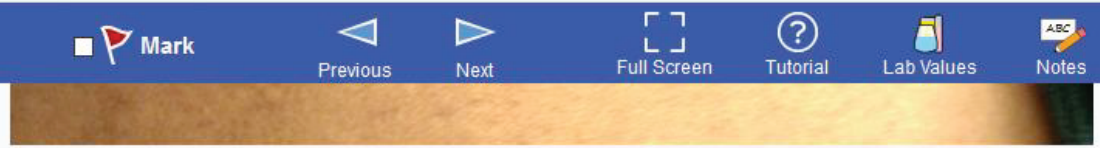
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This patient has new-onset **type 2 diabetes mellitus** (T2DM), which results from a combination of **insulin resistance** and **relative insulin deficiency**. The early course of T2DM is characterized by increased insulin production and decreased sensitivity of target organs to the effects of insulin, although insulin levels

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This patient has new-onset **type 2 diabetes mellitus** (T2DM), which results from a combination of **insulin resistance** and **relative insulin deficiency**. The early course of T2DM is characterized by increased insulin production and decreased sensitivity of target organs to the effects of insulin, although insulin levels may later decline as the disease progresses. In addition, this patient has acanthosis nigricans, which is another sign of insulin resistance.

Insulin resistance in adipose cells hinders the antilipolytic effects of insulin, leading to lipolysis and release of free fatty acids. In turn, chronically **elevated free fatty acid levels** contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis. Other factors that contribute to insulin resistance include obesity and a sedentary lifestyle.

(Choice A) Absolute insulin deficiency in type 1 diabetes mellitus leads to increased gluconeogenesis and conversion of fatty acids to ketone bodies (eg, beta-hydroxybutyrate). Very high levels of ketone bodies are seen in diabetic ketoacidosis but are not typical in T2DM and do not interfere with the production or actions of insulin.

(Choice B) C-peptide is secreted with insulin in equimolar amounts from pancreatic beta cells. Patients with insulin resistance will have increased production of both insulin and C-peptide, but C-peptide does not

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conversion of fatty acids to ketone bodies (eg, beta-hydroxybutyrate). Very high levels of ketone bodies are seen in diabetic ketoacidosis but are not typical in T2DM and do not interfere with the production or actions of insulin.

(Choice B) C-peptide is secreted with insulin in equimolar amounts from pancreatic beta cells. Patients with insulin resistance will have increased production of both insulin and C-peptide, but C-peptide does not cause insulin resistance.

(Choices D and E) The "metabolic syndrome" is a common collection of clinical features that includes elevated triglycerides, low HDL cholesterol, central obesity, hypertension, and elevated glucose. These patients typically have significant insulin resistance. However, elevated LDL and HDL levels do not contribute to insulin resistance or acanthosis nigricans.

Educational objective:

Type 2 diabetes mellitus is due to insulin resistance and relative insulin deficiency. Chronically elevated free fatty acid levels contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis.

References

- Free fatty acids and skeletal muscle insulin resistance.

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A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high school soccer team and also frequently competes in local beauty pageants. The patient follows strict dietary limitations and exercises strenuously 2 hours a day. Onset of menses was at age 13, but her last menstrual period was 8 months ago. She otherwise feels well. Her height is 165 cm (5 ft 5 in) and her weight is 45.3 kg (100 lb), with a BMI of 16.6 kg/m^2. Physical examination shows a pale and thin girl with fine hair around her trunk, but the remainder is otherwise normal. Urine pregnancy test is negative. Which of the following is the most likely mechanism of her amenorrhea?

A. Hyperprolactinemia
B. Hyperthyroidism
C. Hypothalamic suppression
D. Primary ovarian failure
E. Primary pituitary dysfunction

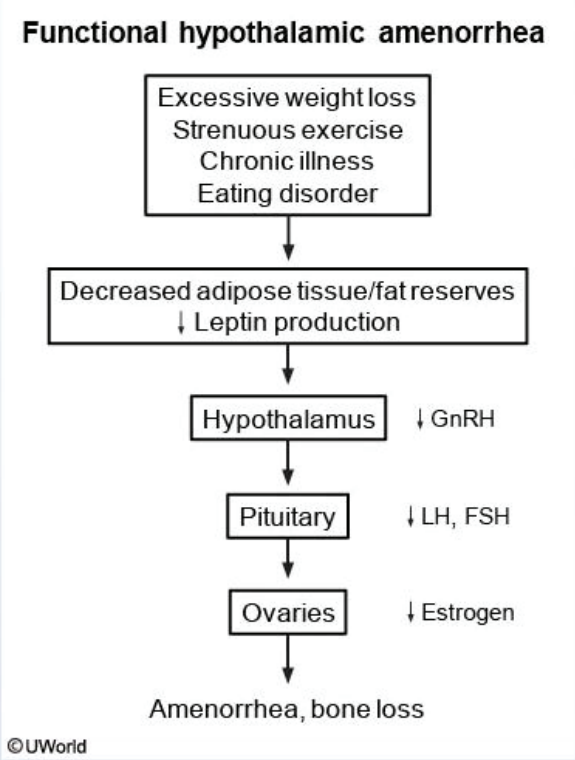
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A. Hyperprolactinemia (3%)
B. Hyperthyroidism (3%)
C. Hypothalamic suppression (80%)
D. Primary ovarian failure (7%)
E. Primary pituitary dysfunction (6%)

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Amenorrhea can be categorized as primary (failure of menarche prior to age 15) or secondary (cessation of menstruation in premenopausal women who previously have had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient has **secondary amenorrhea** associated with low body weight, frequent strenuous exercise, and lanugo (fine hair indicating inadequate caloric intake), suggesting **functional hypothalamic amenorrhea** (FHA). FHA is commonly seen in competitive athletes, dancers, fashion models, and others who maintain very low body weights. The underlying pathophysiology of FHA is incompletely understood but appears to involve reduced circulating **leptin** levels as a result of diminished adipose tissue stores. The decrease in leptin levels inhibits **pulsatile gonadotropin-releasing hormone (GnRH) release** from the hypothalamus, causing decreased pituitary LH and FSH secretion, low circulating estrogen levels, and amenorrhea.

(Choice A) Like FHA, hyperprolactinemia can cause secondary amenorrhea by suppressing normal GnRH release in the hypothalamus. Affected women may also develop galactorrhea. However, this patient's low body weight, caloric restriction, and strenuous exercise regimen are more consistent with FHA.

(Choice B) Hyperthyroidism can cause irregular menses or amenorrhea, along with weight loss. However, this patient has no other features to suggest a thyroid disorder (eg, goiter, temperature intolerance,

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(Choice B) Hyperthyroidism can cause irregular menses or amenorrhea, along with weight loss. However, this patient has no other features to suggest a thyroid disorder (eg, goiter, temperature intolerance, diarrhea, hair loss).

(Choices D and E) The amenorrhea in patients with FHA stems from a deficiency in hypothalamic GnRH release, rather than a problem with the pituitary or ovaries; this patient has no other features of hypopituitarism.

Educational objective:
Functional hypothalamic amenorrhea results from loss of pulsatile gonadotropin-releasing hormone release from the hypothalamus and is caused by weight loss, strenuous exercise, systemic illness, or abnormal eating habits. Loss of cyclic gonadotropin release leads to a decrease in LH and FSH secretion from the pituitary, which in turn causes low circulating estrogen levels.

References

- Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations.

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www.ncbi.nlm.nih.gov/pubmed/18224538

A 27-year-old woman comes to the office for evaluation of infertility. The patient and her husband have been trying to conceive for the past 2 years but have been unsuccessful. Her husband recently underwent infertility evaluation and was found to have no abnormalities. The patient's menses began at age 13, and her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

A. Hypothalamic neurons
B. Ovarian granulosa cells
C. Ovarian theca cells
D. Pituitary lactotrophs

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been trying to conceive for the past 2 years but have been unsuccessful. Her husband recently underwent infertility evaluation and was found to have no abnormalities. The patient's menses began at age 13, and her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

A. Hypothalamic neurons
B. Ovarian granulosa cells
C. Ovarian theca cells
D. Pituitary lactotrophs
E. Pituitary somatotrophs

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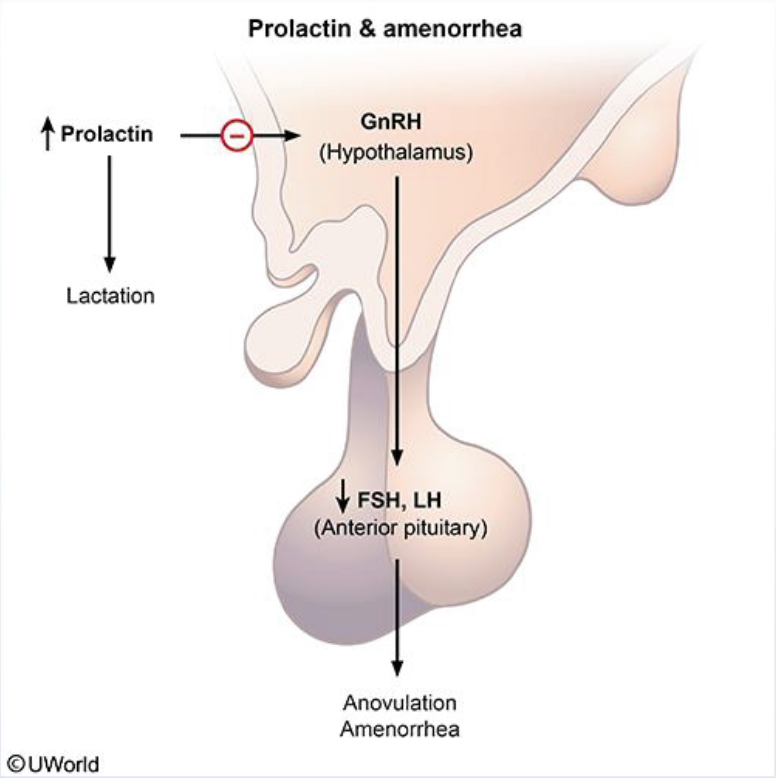
her menstrual cycles were regular until the last few years, when they began occurring at intervals of 3-4 months. She has occasional headaches but no other symptoms. The patient has no prior medical conditions and takes no medications. On physical examination, the patient appears normal and has well-developed secondary sexual characteristics. Cardiopulmonary and abdominal examinations are normal. Pelvic examination reveals no adnexal masses. Neurological examination shows diminished vision in the bilateral temporal visual fields. Examination of the other cranial nerves is normal and there is no focal weakness or sensory loss. An abnormality originating in which of the following is the most likely cause of this patient's current condition?

A. Hypothalamic neurons (3%)
B. Ovarian granulosa cells (0%)
C. Ovarian theca cells (1%)
✓ D. Pituitary lactotrophs (85%)
E. Pituitary somatotrophs (8%)

85%
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02/12/2021

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This patient's symptoms are concerning for a **pituitary tumor**. Large pituitary tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can lead to bitemporal hemianopsia.

The most common type of pituitary adenoma is a **prolactinoma**. Prolactin is a peptide hormone secreted from lactotrophs of the pituitary gland whose primary physiologic action is maintenance of lactation in postpartum women. Hyperprolactinemia also **suppresses GnRH production** in the hypothalamus, leading to **oligomenorrhea/amenorrhea** and infertility. Suppression of ovulation is also seen as a physiologic effect of breastfeeding, which supports elevated prolactin levels for 6 months or more postpartum.

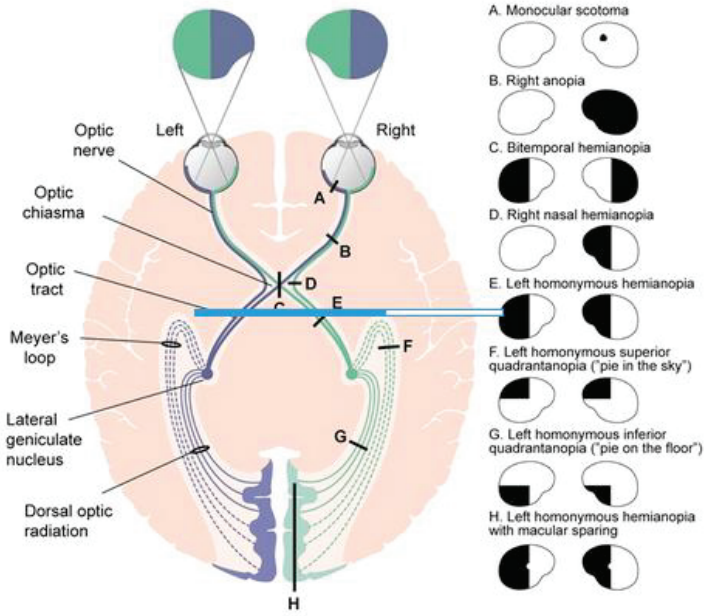
(Choice A) Kallmann syndrome is a disorder involving the GnRH-producing neurons in the hypothalamus. In addition to decreased sense of smell (anosmia/hyposomia), this condition causes hypogonadotropic hypogonadism and presents with short stature and delayed puberty (primary amenorrhea). This patient has secondary amenorrhea (ie, normal initial onset of puberty followed by menstrual dysregulation), and her bilateral temporal visual deficits are more suggestive of a pituitary rather than hypothalamic lesion.

(Choice B) Ovarian granulosa cells produce estrogen, progesterone, and inhibin. Loss of these cells (eg, due to autoimmune disorder) can lead to primary ovarian insufficiency and present with infertility and

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Exhibit Display

Visual pathways from above



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due to autoimmune disorder) can lead to primary ovarian insufficiency and present with infertility and

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her bilateral temporal visual deficits are more suggestive of a pituitary rather than hypothalamic lesion.

(Choice B) Ovarian granulosa cells produce estrogen, progesterone, and inhibin. Loss of these cells (eg, due to autoimmune disorder) can lead to primary ovarian insufficiency and present with infertility and secondary amenorrhea. However, patients often have hypoestrogenic symptoms (eg, hot flashes), and this disorder would not cause visual field defects.

(Choice C) Ovarian theca cells produce androgens, which provide the substrate for subsequent synthesis of estrogens. Amenorrhea and infertility related to hyperactivity of these cells are typically associated with signs of hyperandrogenism (eg, hirsutism).

(Choice E) Unlike most pituitary hormones, which are under positive regulation by the hypothalamus, prolactin is primarily under negative regulation by hypothalamic dopaminergic neurons via the pituitary stalk. Because of this, any pituitary tumor of significant size that disrupts these dopaminergic pathways can cause moderate hyperprolactinemia. However, somatotroph adenomas typically cause acromegaly, with prognathism and bony enlargement of the hands and feet.

Educational objective:
Prolactinomas are the most common pituitary adenoma and can cause galactorrhea, menstrual irregularities, and infertility in premenopausal women. Large pituitary adenomas can cause headaches

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Educational objective:

Prolactinomas are the most common pituitary adenoma and can cause galactorrhea, menstrual irregularities, and infertility in premenopausal women. Large pituitary adenomas can cause headaches from mass effect and bitemporal hemianopsia from compression of the optic chiasm.

References

- Progress in the diagnosis and classification of pituitary adenomas.

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Fifty obese adults without diabetes mellitus are enrolled in a 10-week weight loss program. The program includes a low-calorie diet and moderate-intensity exercise for at least 150 minutes per week. The study subjects who are adherent to the regimen lose an average of 7 kg (15.5 lb) at the end of 10 weeks. Venous blood samples to study biochemical changes induced by weight loss are taken at the start of the trial and at the 10-week follow-up visit. Which of the following hormonal changes are likely to occur during the course of the study?

	Ghrelin	Leptin	Insulin
A.	↑	↓	↓
B.	↓	↓	↓
C.	↓	↑	↑
D.	↑	↓	↑
E.	↑	↑	↓

Submit

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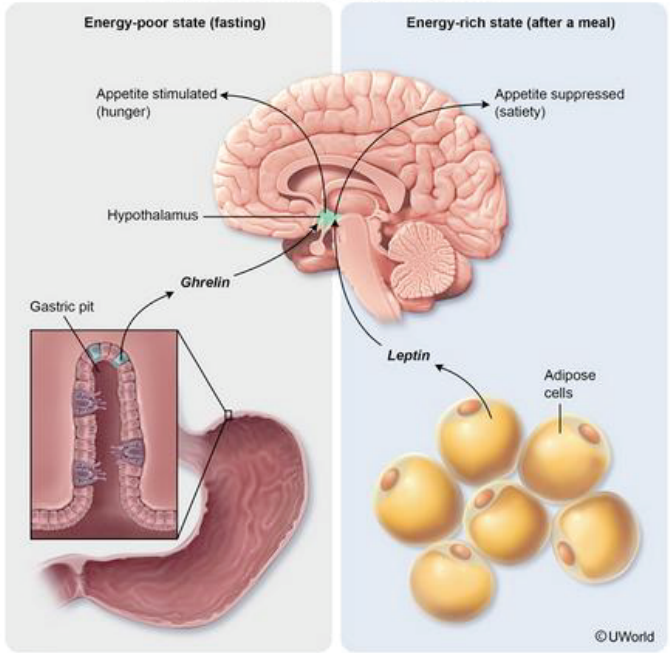
	Ghrelin	Leptin	Insulin	
✓ A.	↑	↓	↓	(44%)
B.	↓	↓	↓	(11%)
C.	↓	↑	↑	(28%)
D.	↑	↓	↑	(8%)
E.	↑	↑	↓	(6%)

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Explanation

Exhibit Display

Appetite hormones: leptin & ghrelin



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Energy homeostasis and body fat content are regulated by a complex network of hormones. Prominent hormones involved in weight regulation include:

- **Ghrelin:** Produced primarily in the stomach in response to fasting, ghrelin stimulates appetite and promotes weight gain.
- **Leptin:** Produced primarily by fat cells in response to short-term food intake and long-term adequacy of fat stores, leptin acts on the hypothalamus to decrease appetite (obesity blunts this action). During fasting states, leptin levels fall.
- **Insulin:** Produced by pancreatic beta cells in response to high blood glucose levels, insulin acts on the CNS to decrease appetite, in addition to its effects on glucose metabolism. Levels are higher and effects are blunted in obesity (insulin resistance); weight loss is associated with greater insulin sensitivity and lower insulin levels.

Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin** levels. This causes an increase in appetite and, typically, regain of weight. The effect can last up to a year or more and accounts for much of the difficulty patients have in

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Caloric restriction and falling fat stores, as in these study subjects, lead to **increased ghrelin** levels along with **decreased insulin and leptin** levels. This causes an increase in appetite and, typically, regain of weight. The effect can last up to a year or more and accounts for much of the difficulty patients have in maintaining short-term weight loss.

(Choice B) Certain bariatric procedures that alter stomach capacity (eg, sleeve gastrectomy) can induce weight loss with decreased ghrelin production (may reduce weight loss-associated appetite stimulation). However, dietary modification and exercise alone would lead to increased ghrelin secretion.

(Choice C) Overeating and weight gain suppress ghrelin secretion and increase secretion of leptin and insulin.

(Choice D) HIV-associated lipodystrophy is an alteration in fat distribution, most often seen in patients receiving highly active antiretroviral therapy. Numerous metabolic abnormalities have been seen in this disorder, including increased insulin levels, increased ghrelin, and decreased leptin secretion.

(Choice E) Fasting states that stimulate ghrelin and suppress insulin secretion generally lead to lower, not higher, leptin levels.

Educational objective:
Ghrelin stimulates appetite and promotes weight gain. Leptin and insulin act in the CNS to decrease

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(Choice E) Fasting states that stimulate ghrelin and suppress insulin secretion generally lead to lower, not higher, leptin levels.

Educational objective:

Ghrelin stimulates appetite and promotes weight gain. Leptin and insulin act in the CNS to decrease appetite. Caloric restriction leads to increased ghrelin levels along with decreased insulin and leptin levels, causing an increase in appetite that can make it difficult to maintain weight loss.

References

- Long-term persistence of hormonal adaptations to weight loss.

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A 43-year-old woman volunteers for a clinical trial testing a medication for type 2 diabetes mellitus. She was diagnosed with diabetes mellitus 5 years ago, and her blood sugar has recently been uncontrolled despite taking the maximum tolerated dose of metformin. The subject's medical history is otherwise unremarkable, and she takes no concurrent medications that would disqualify her from enrolling in the trial. Initial laboratory studies show a fasting glucose of 155 mg/dL and hemoglobin A1c of 8.2%. A urine pregnancy test is negative, and other screening tests are normal. The study drug activates peroxisome proliferator-activated receptor gamma, a nuclear receptor and transcription factor. Activation of this receptor would most likely result in which of the following metabolic changes?

A. Decreased insulin resistance
B. Downregulation of adiponectin
C. Increased free fatty acid levels
D. Increased insulin release
E. Upregulation of leptin activity

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- A. Decreased insulin resistance (59%)
- B. Downregulation of adiponectin (10%)
- C. Increased free fatty acid levels (13%)
- D. Increased insulin release (11%)
- E. Upregulation of leptin activity (5%)

Correct

59%
Answered correctly

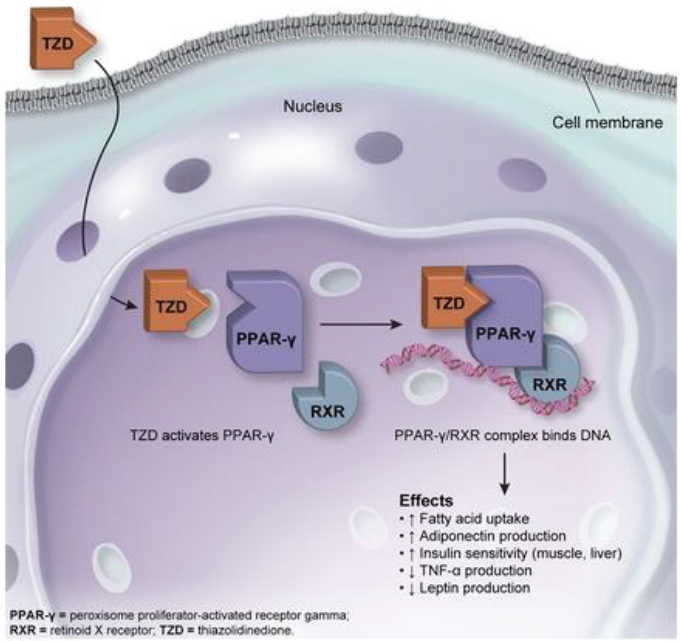
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Exhibit Display

Thiazolidinedione mechanism of action



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This clinical trial is studying a **thiazolidinedione** (TZD), a class of medications that **decrease insulin resistance**. TZDs (eg, pioglitazone) bind to **peroxisome proliferator-activated receptor gamma** (PPAR-γ), a transcriptional regulator of genes involved in glucose and lipid metabolism. The activated complex then binds to the transcriptional regulatory sequence of target genes; important genes upregulated by TZDs include:

- **Glucose transporter-4**, an insulin-responsive, transmembrane glucose transporter expressed in adipocytes and skeletal myocytes that increases glucose uptake by target cells
- **Adiponectin**, a cytokine secreted by fat tissue that increases the number of insulin-responsive adipocytes and stimulates fatty acid oxidation **(Choice B)**

TZDs are functionally similar to fibrate medications (eg, fenofibrate, gemfibrozil), which bind PPAR-α and are effective in lowering blood triglyceride levels. The PPAR family of transcriptional regulators also plays a significant role in the pathogenesis of metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance).

(Choice C) PPAR-γ activation leads to an increase in fat mass secondary to the increased differentiation of preadipocytes into mature adipocytes. The increased movement of free fatty acids into fat cells, along

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(Choice C) PPAR-γ activation leads to an increase in fat mass secondary to the increased differentiation of preadipocytes into mature adipocytes. The increased movement of free fatty acids into fat cells, along with increased fatty acid oxidation (adiponectin effect), causes circulating free fatty acid levels to decrease.

(Choice D) TZDs do not stimulate insulin secretion; rather, as insulin resistance diminishes, circulating levels of insulin tend to decrease over time.

(Choice E) Leptin is a hormone secreted by fat cells that acts on the hypothalamus to decrease appetite. Although PPAR-γ activation increases fat cell mass, circulating leptin levels remain unchanged or decrease due to the inhibiting effect of PPAR-γ on leptin gene transcription.

Educational objective:
Thiazolidinediones (TZDs) lower blood glucose by decreasing insulin resistance. TZDs activate peroxisome proliferator-activated receptor gamma, a nuclear receptor that alters the transcription of genes involved in glucose and lipid metabolism.

References

- Minireview: challenges and opportunities in development of PPAR agonists.
- The roles of peroxisome proliferator-activated receptors in the metabolic syndrome.

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A 48-year-old woman with a complex medical history comes to the clinic due to a change in her body habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

A. Antiretroviral medication
B. HMG-CoA reductase inhibitor
C. Loop diuretic
D. Nonsteroidal antiinflammatory drug
E. Proton pump inhibitor
F. Selective serotonin reuptake inhibitor

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habitus. She says her legs are "like sticks" while her "belly is getting bigger." The patient also feels increasingly fatigued but does not have excessive daytime somnolence. She has been homeless for much of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

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B. HMG-CoA reductase inhibitor
C. Loop diuretic
D. Nonsteroidal antiinflammatory drug
E. Proton pump inhibitor
F. Selective serotonin reuptake inhibitor
G. Thyroperoxidase inhibitor

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of the last 5 years but has been living in a residential care facility for the last 12 months. On physical examination, she is distractible and has an inappropriate affect but is cooperative. Neurologic and mental status examination is otherwise normal. There is loss of adipose tissue from the extremities and face, with a noticeable increase in abdominal girth. Which of the following types of medications is most likely to be responsible for this patient's symptoms?

- A. Antiretroviral medication (53%)
- B. ~~HMG-CoA reductase inhibitor~~ (7%)
- C. ~~Loop diuretic~~ (2%)
- D. ~~Nonsteroidal antiinflammatory drug~~ (3%)
- E. ~~Proton pump inhibitor~~ (1%)
- F. ~~Selective serotonin reuptake inhibitor~~ (11%)
- G. Thyroperoxidase inhibitor (20%)

Correct

53%

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This patient has **redistribution of fat** from the extremities to the trunk. Medication-induced body fat redistribution (sometimes called **lipoatrophy** or **lipodystrophy**) is a common adverse effect of **highly-active antiretroviral therapy (HAART)** and can be considered a product of 2 independent processes: wasting of fat from the face and extremities and deposition of fat in the trunk and viscera.

1. **Lipoatrophy** refers to loss of subcutaneous fat, especially from the face, extremities, and buttocks. It is primarily seen in patients taking nucleoside reverse transcriptase inhibitors (mainly stavudine and zidovudine) and is also associated with protease inhibitor use.
2. **Central fat deposition** also occurs in some patients and causes increased abdominal girth and a buffalo hump (dorsocervical fat accumulation) that is similar to Cushing syndrome. Central fat deposition may be seen with any HIV treatment regimen and may be a result of treating HIV rather than a specific medication adverse effect.

Both syndromes have been associated with **metabolic abnormalities** including insulin resistance, hypertriglyceridemia, and reduced HDL cholesterol levels.

(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

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(Choice B) HMG-CoA reductase inhibitors (statins) are associated with myalgias and an increase in hepatic transaminase levels. They do not cause fat redistribution.

(Choice C) Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide) can cause hyperglycemia and hypertriglyceridemia and may have a small effect on fat distribution. However, these effects have not been seen with loop diuretics (eg, furosemide).

(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism. Common side effects include bone marrow suppression (eg, anemia, agranulocytosis).

Educational objective:
Highly-active antiretroviral therapy (HAART) for HIV is commonly associated with body fat redistribution.

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(Choice D) Unlike glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs) do not significantly alter tissue lipid metabolism or cause fat redistribution.

(Choice E) Proton pump inhibitors (PPIs) are used to reduce gastric acid secretion in patients with peptic ulcer and gastroesophageal reflux. PPIs can cause hypomagnesemia and increased risk of osteoporosis.

(Choice F) Selective serotonin reuptake inhibitors are indicated for treatment of depression and chronic anxiety. They can cause weight gain in a subset of patients but have not been linked to fat redistribution.

(Choice G) Thyroperoxidase inhibitors (eg, methimazole, propylthiouracil) are used to treat hyperthyroidism. Common side effects include bone marrow suppression (eg, anemia, agranulocytosis).

Educational objective:
Highly-active antiretroviral therapy (HAART) for HIV is commonly associated with body fat redistribution. Subcutaneous lipoatrophy involving the face and extremities is associated with nucleoside reverse transcriptase inhibitors (especially stavudine and zidovudine) and protease inhibitors. Central fat accumulation in the trunk and viscera can occur with any HAART regimen.

References

- Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction.

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A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patient was evaluated for recurrent, brief episodes of excessive warmth and sweating, which were interfering with her usual activities. Thyroid hormone levels were normal, and the patient was subsequently diagnosed with menopausal hot flashes. Treatment with estrogen-containing hormone replacement therapy was begun with significant symptom improvement. She has no other medical conditions and takes no other medications. Which of the following most likely occurred in this patient as a result of her medication use?

A. Decreased conversion of T4 to T3
B. Decreased thyroid iodine uptake
C. Decreased TSH level
D. Increased free T3 level
E. Increased total T4 level

Submit

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A 52-year-old, post-menopausal woman comes to the office for a follow-up appointment. Six months ago, the patient was evaluated for recurrent, brief episodes of excessive warmth and sweating, which were interfering with her usual activities. Thyroid hormone levels were normal, and the patient was subsequently diagnosed with menopausal hot flashes. Treatment with estrogen-containing hormone replacement therapy was begun with significant symptom improvement. She has no other medical conditions and takes no other medications. Which of the following most likely occurred in this patient as a result of her medication use?

A. ~~Decreased conversion of T4 to T3~~ (18%)
B. ~~Decreased thyroid iodine uptake~~ (3%)
C. Decreased TSH level (31%)
D. Increased free T3 level (6%)
E. Increased total T4 level (39%)

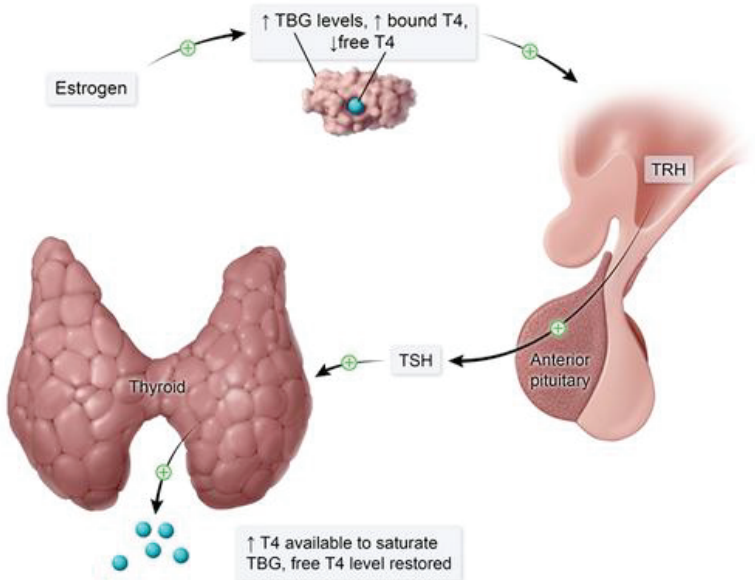
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Estrogen effect on thyroid hormone production



TBG = thyroxine-binding globulin.

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Circulating thyroid hormone consists of 2 fractions: an inert **protein-bound** fraction and a **free fraction** that is available to enter target cells via a carrier-mediated mechanism. More than 99% of circulating thyroid hormone is bound to plasma proteins, creating a large circulating reservoir of thyroid hormone. **Thyroxine-binding globulin** (TBG) accounts for approximately 70% of thyroid hormone binding with an additional share bound by albumin and transthyretin.

An **increase in estrogen activity** (eg, pregnancy, oral contraceptive use, postmenopausal hormone replacement therapy) **raises circulating TBG levels**, causing a corresponding reduction in free T4 and T3 levels. In patients with a normal hypothalamic-pituitary-thyroid axis, this reduction will result in a transient increase in TSH, leading to increased thyroid hormone production until the additional TBG becomes saturated with thyroid hormone and free T4 and T3 levels are restored (ie, patients remain **euthyroid**). Therefore, an increase in the TBG level leads to an **increase in total T4** and T3 (bound plus free fractions).

(Choice A) Estrogen does not affect the peripheral conversion of T4 to T3. Medications that decrease the peripheral conversion of T4 to T3 include propylthiouracil, glucocorticoids, and nonselective beta blockers.

(Choices B and C) Thyroid iodine uptake *increases* transiently due to the temporary *rise* in TSH that occurs with increased TBG synthesis. However, iodine uptake normalizes once the newly synthesized

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(Choice A) Estrogen does not affect the peripheral conversion of T4 to T3. Medications that decrease the peripheral conversion of T4 to T3 include propylthiouracil, glucocorticoids, and nonselective beta blockers.

(Choices B and C) Thyroid iodine uptake *increases* transiently due to the temporary *rise* in TSH that occurs with increased TBG synthesis. However, iodine uptake normalizes once the newly synthesized TBG becomes saturated with thyroid hormone and TSH returns to normal.

(Choice D) Increased circulating TBG levels cause a transient *drop* in free T4 and T3 levels as the existing pool of thyroid hormone becomes more protein-bound. However, free T4 and T3 levels quickly normalize as the thyroid synthesizes an appropriate quantity of new thyroid hormone to saturate the additional TBG.

Educational objective:
An increase in estrogen activity, as seen in pregnancy or postmenopausal estrogen replacement therapy, increases the level of thyroxine-binding globulin. This leads to an increase in total thyroid hormone levels, but feedback control maintains normal levels of free (biologically active) thyroid hormone.

Pharmacology	Endocrine, Diabetes & Metabolism	Menopause
Subject	System	Topic

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A 43-year-old woman comes to the office due to increasing fatigue and weight gain despite decreased food intake. She states, "I have not been feeling like myself lately." The patient asks to be referred to a dermatologist as she has always had "nice" skin that has now become dry. Her hair has been thinning and she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

	TSH	T3	Reverse T3	T4
A.	No change	Increase	Increase	Decrease
B.	No change	Increase	Decrease	Decrease
C.	Decrease	Increase	Increase	Decrease
D.	Decrease	Increase	Decrease	Decrease
E.	Decrease	Increase	Decrease	Increase

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intake. She states, "I have not been feeling like myself lately." The patient asks to be referred to a dermatologist as she has always had "nice" skin that has now become dry. Her hair has been thinning and she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

	TSH	T3	Reverse T3	T4
A.	No change	Increase	Increase	Decrease
B.	No change	Increase	Decrease	Decrease
C.	Decrease	Increase	Increase	Decrease
D.	Decrease	Increase	Decrease	Decrease
E.	Decrease	Increase	Decrease	Increase

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she hopes that a dermatologist can help with that too. Laboratory evaluation shows high serum TSH, low triiodothyronine (T3), and low thyroxine (T4) levels. The patient has a family member with fatigue whose energy level increased after liothyronine (T3) supplementation, and she asks to try this medication. Administering this therapy would most likely result in which of the following hormone level changes in this patient?

	TSH	T3	Reverse T3	T4	
A.	~~No change~~	~~Increase~~	~~Increase~~	~~Decrease~~	(3%)
B.	~~No change~~	~~Increase~~	~~Decrease~~	~~Decrease~~	(4%)
C.	Decrease	Increase	Increase	Decrease	(26%)
✓ D.	Decrease	Increase	Decrease	Decrease	(48%)
E.	~~Decrease~~	~~Increase~~	~~Decrease~~	~~Increase~~	(17%)

Correct

48%

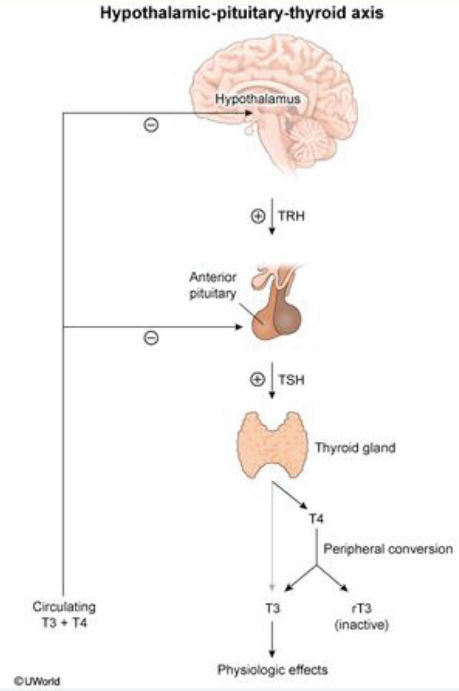
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Circulating thyroid hormone exists in 3 primary forms:

1. **T4 (thyroxine)** is the major secretory product of the thyroid gland.
2. **T3 (triiodothyronine)** is the most active form of thyroid hormone; a small amount is released by the thyroid gland, but the majority arises from peripheral deiodination of T4.
3. **Reverse T3 (rT3)** is an inactive form that is generated almost entirely from the peripheral conversion of T4.

The hypothalamus-pituitary-thyroid axis is regulated via **negative feedback** by thyroid hormone on thyrotropin-releasing hormone–secreting neurons in the hypothalamus and thyrotrophs of the anterior pituitary. In the normal state, most of the circulating thyroid hormone is in the form of T4, which provides most of the feedback suppression of TSH release. However, T3 also suppresses TSH.

This patient has primary hypothyroidism, with low thyroid hormone (T3 and T4) and elevated TSH levels. Exogenous T3 supplementation **rapidly suppresses TSH** levels by increasing negative feedback, which in turn decreases T4 secretion from the thyroid gland. Furthermore, rT3 also decreases because less T4 is available for conversion (T3 cannot be converted into rT3).

However, synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it

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Exogenous T3 supplementation **rapidly suppresses TSH** levels by increasing negative feedback, which in turn decreases T4 secretion from the thyroid gland. Furthermore, rT3 also decreases because less T4 is available for conversion (T3 cannot be converted into rT3).

However, synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it has a short half-life and patients can experience wide fluctuations in plasma T3 levels. T4 (levothyroxine) supplementation provides a more physiologic effect and is preferred.

Educational objective:

TSH from the anterior pituitary stimulates the thyroid to produce thyroxine (T4) and a small amount of triiodothyronine (T3). T4 is converted in peripheral tissues to T3 (active form) and reverse T3 (inactive form). TSH secretion is under negative feedback by thyroid hormone on the hypothalamus and pituitary.

References

- Mini review: thyrotropin-releasing hormone and the thyroid hormone feedback mechanism.

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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A 52-year-old woman comes to the office for follow-up of type 2 diabetes mellitus. The patient was diagnosed with diabetes 6 months ago and initiated intensive lifestyle modification with increased exercise and a calorie-restricted diet; since that time, she has felt better subjectively but has lost only 2 kg (4.4 lb). Vital signs are normal. BMI is 35 kg/m^2. Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%. Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production
A.	Decreased	Increased	Increased
B.	Decreased	Increased	Unchanged
C.	Decreased	Unchanged	Unchanged
D.	Unchanged	Increased	Unchanged

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diagnosed with diabetes 6 months ago and initiated intensive lifestyle modification with increased exercise and a calorie-restricted diet; since that time, she has felt better subjectively but has lost only 2 kg (4.4 lb). Vital signs are normal. BMI is 35 kg/m^2. Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%. Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production
A.	Decreased	Increased	Increased
B.	Decreased	Increased	Unchanged
C.	Decreased	Unchanged	Unchanged
D.	Unchanged	Increased	Unchanged
E.	Unchanged	Unchanged	Increased

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Vital signs are normal. BMI is 35 kg/m². Fasting glucose is 155 mg/dL and hemoglobin A1c is 8.0%.

Serum renal and liver function markers are normal. After discussion with the patient, metformin therapy is initiated. Which of the following physiologic changes are most likely to result as a direct effect of this medication?

	Hepatic gluconeogenesis	Muscle glucose uptake	Endogenous insulin production	
A.	~~Decreased~~	~~Increased~~	~~Increased~~	(11%)
✓ B.	Decreased	Increased	Unchanged	(67%)
C.	~~Decreased~~	~~Unchanged~~	~~Unchanged~~	(16%)
D.	Unchanged	Increased	Unchanged	(3%)
E.	~~Unchanged~~	~~Unchanged~~	~~Increased~~	(0%)

Correct

67%

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Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency

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Precautions/ contraindications	• Hepatic insufficiency • Congestive heart failure

This patient has uncontrolled type 2 diabetes mellitus and is appropriately given metformin, which is the preferred first-line medication for most patients. **Metformin** has a number of important metabolic effects:

- **Reduced hepatic gluconeogenesis** and release of glucose into circulation: Metformin inhibits glycerophosphate dehydrogenase and complex I (mitochondrial enzymes), which reduces the availability of substrates for gluconeogenesis (eg, glycerol, lactate).
- **Increased insulin-dependent peripheral glucose uptake** and utilization.
- Reduced circulating lipid levels: Metformin upregulates AMP-activated protein kinase in hepatocytes, which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest **weight loss** in most patients.

(Choice A) Sulfonylureas (eg, glyburide, glimepiride) stimulate beta cell insulin release, leading to decreased glycogenolysis and gluconeogenesis and increased peripheral uptake of glucose; the higher

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which inhibits lipogenesis.

Circulating levels of endogenous insulin are unchanged or slightly decreased by metformin; therefore, metformin carries **low risk of hypoglycemia**. In addition, it reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest **weight loss** in most patients.

(Choice A) Sulfonylureas (eg, glyburide, glimepiride) stimulate beta cell insulin release, leading to decreased glycogenolysis and gluconeogenesis and increased peripheral uptake of glucose; the higher circulating insulin levels also confer an increased risk of hypoglycemia and weight gain.

Educational objective:
Metformin reduces hepatic gluconeogenesis and release of glucose into circulation; increases peripheral glucose uptake and utilization; and reduces circulating lipid levels. Circulating insulin levels are unchanged or slightly decreased; therefore, metformin carries low risk of hypoglycemia. In addition, metformin reduces caloric intake due to decreased appetite and decreased absorption of glucose, leading to modest weight loss.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 13-year-old boy is evaluated for abnormal growth. His mother says that he has grown rapidly over the past 10 months and is much taller than his older brother and other children his age. During this time, she has had a hard time finding clothes that fit him and has had to buy new shoes for him each month due to increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

A. Aneuploidy of the X chromosome
B. De novo mutation in the fibrillin-1 gene
C. Defective growth hormone receptor
D. Excessive liver production of IGF-1
E. Excessive thyroxine production

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increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

- A. Aneuploidy of the X chromosome
- B. De novo mutation in the fibrillin-1 gene
- C. Defective growth hormone receptor
- D. Excessive liver production of IGF-1
- E. Excessive thyroxine production
- F. Increased hypothalamic release of IGF-1
- G. Increased pituitary gonadotropin release

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increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

- A. Aneuploidy of the X chromosome (3%)
- B. De novo mutation in the fibrillin-1 gene (5%)
- C. Defective growth hormone receptor (5%)
- ✓ D. Excessive liver production of IGF-1 (58%)
- E. Excessive thyroxine production (1%)
- F. Increased hypothalamic release of IGF-1 (13%)
- G. Increased pituitary gonadotropin release (11%)

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This patient most likely has **gigantism**, a condition caused by hypersecretion of **growth hormone (GH)** during childhood. GH is a peptide hormone secreted by the anterior pituitary that acts as both a growth promoter and stress hormone (increasing glucose and free fatty acid levels). Although GH has direct effects on target tissue (eg, chondrogenesis, myocyte protein synthesis), its growth-promoting effects are primarily mediated by **insulin-like growth factor-1 (IGF-1)**, which is released from the liver following stimulation of hepatic GH receptors. IGF-1 binds to a specific receptor tyrosine kinase and stimulates cell growth and proliferation in bone, cartilage, skeletal muscle, and other soft tissues.

Gigantism occurs in children and adolescents before fusion of the epiphyseal growth plates, resulting in **rapid linear growth** along with large hands and feet, thickening of the calvarium, protrusion of the jaw (**prognathism**), excessive sweating, and oily skin. The adult variant, acromegaly, has no effect on stature because the epiphyseal growth plates have already fused.

(Choices A and B) Klinefelter syndrome is caused by a nondisjunction of sex chromosomes (47,XXY). Patients are phenotypically male with hypogonadism and infertility. Marfan syndrome is caused by a defect in fibrillin-1 and presents with joint hypermobility, increased limb length, and arachnodactyly. These disorders are associated with tall stature but do not exhibit prognathism or bony enlargement of the hands and feet.

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and feet.

(Choice C) Defects in the GH receptor cause Laron dwarfism, characterized by decreased linear growth, high serum GH concentrations, and low levels of circulating IGF-1.

(Choice E) Excessive thyroxine production (ie, hyperthyroidism) presents with weight loss, heat intolerance, and tremor. Sweating is common, but hyperthyroidism in children causes short stature, not accelerated growth.

(Choice F) Circulating levels of IGF-1 are produced primarily in the liver. Although IGF-1 is also produced locally in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

(Choice G) Increased pituitary gonadotropin release causes central precocious puberty. This patient has appropriate sexual development for age.

Educational objective:
Gigantism is caused by excess growth hormone (GH) during childhood and is characterized by accelerated linear growth, prognathism, and bony enlargement of the hands and feet. GH excess after closure of the epiphysial growth plates causes acromegaly. GH has direct effects on target tissues and indirect effects mediated by insulin-like growth factor-1 secretion from the liver.

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A 64-year-old man comes to the office due to a 6-month history of difficulty urinating, with frequent straining and dribbling. His symptoms have increased over time and affect his quality of life significantly. The physician prescribes a drug that gives the patient moderate symptomatic relief. However, he also experiences a decrease in libido and impaired erectile function. Which of the following is the most likely mechanism of action of this patient's medication?

- A. Decreased dihydrotestosterone synthesis
- B. Decreased Leydig cell androgen synthesis
- C. Decreased Leydig cell stimulation by LH
- D. Decreased peripheral androgen aromatization
- E. Impaired androgen-receptor interaction
- F. Impaired second messenger action

Submit

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A 64-year-old man comes to the office due to a 6-month history of difficulty urinating, with frequent straining and dribbling. His symptoms have increased over time and affect his quality of life significantly. The physician prescribes a drug that gives the patient moderate symptomatic relief. However, he also experiences a decrease in libido and impaired erectile function. Which of the following is the most likely mechanism of action of this patient's medication?

- A. Decreased dihydrotestosterone synthesis (57%)
- B. Decreased Leydig cell androgen synthesis (5%)
- C. Decreased Leydig cell stimulation by LH (6%)
- D. Decreased peripheral androgen aromatization (8%)
- E. Impaired androgen-receptor interaction (14%)
- F. Impaired second messenger action (8%)

Correct

57% Answered correctly

43 secs Time Spent

10/13/2020 Last Updated

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This patient has **benign prostatic hyperplasia** (BPH) with lower urinary tract symptoms (eg, hesitancy, dribbling). BPH is characterized by an increase in glandular volume, which obstructs urine flow in the prostatic urethra. Prostate enlargement in BPH is driven primarily by **dihydrotestosterone** (DHT), which is derived from testosterone by **5-alpha-reductase** (5AR) in peripheral tissues. DHT has a much higher affinity than testosterone for the androgen receptor and mediates the majority of testosterone effects.

5AR inhibitors (eg, finasteride) are antiandrogen agents that reduce conversion of testosterone to DHT. In men with BPH, 5AR inhibitors induce a gradual **reduction in prostate volume**, improving urinary flow. However, they are associated with significant **androgen-deficiency effects**, including decreased libido, erectile dysfunction, and decreased ejaculate volume. In addition, the residual testosterone is available for conversion by aromatase to estradiol, leading to gynecomastia.

(Choices B and C) Long-acting gonadotropin-releasing hormone (GnRH) analogues (eg, leuprolide) suppress pituitary LH secretion, leading to decreased testosterone production in Leydig cells. Steroid synthesis inhibitors (eg, ketoconazole) directly reduce testosterone production in the testes. However, 5AR inhibitors affect peripheral testosterone metabolism, not testosterone production.

(Choice D) Aromatase inhibitors (eg, anastrozole) decrease conversion of androgens to the corresponding

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synthesis inhibitors (eg, ketoconazole) directly reduce testosterone production in the testes. However, 5AR inhibitors affect peripheral testosterone metabolism, not testosterone production.

(Choice D) Aromatase inhibitors (eg, anastrozole) decrease conversion of androgens to the corresponding estrogens and are primarily used in treatment of hormone receptor–positive breast cancer in women. These agents are not used for BPH.

(Choice E) The interaction of testosterone and DHT with the androgen receptor is inhibited by flutamide and spironolactone. These agents have significant feminizing effects (eg, gynecomastia) and are not used in BPH.

(Choice F) The androgen receptor primarily acts as a DNA-binding transcription factor and does not require second messenger action. 5AR inhibitors do not have a significant effect on second messenger systems.

Educational objective:
5-alpha-reductase inhibitors (eg, finasteride) reduce conversion of testosterone to dihydrotestosterone. In men with benign prostatic hyperplasia, these agents reduce prostate volume and alleviate obstruction of urinary flow. However, they are associated with androgen-deficiency effects, including decreased libido, erectile dysfunction, and decreased ejaculate volume.

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A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

A. Levothyroxine
B. Potassium iodide
C. Prednisone
D. Propranolol
E. Propylthiouracil

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A nuclear waste disposal plant suffers a containment failure and several grams of iodine-131 are released into the local environment. A number of workers are believed to have been exposed to dangerous levels of the radioactive material. Which of the following should be immediately administered to help prevent tissue damage in these individuals?

- A. Levothyroxine (6%)
- ✓ B. Potassium iodide (67%)
- C. Prednisone (1%)
- D. Propranolol (1%)
- E. Propylthiouracil (23%)

Correct

67% Answered correctly

12 secs Time Spent

09/12/2020 Last Updated

Explanation

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Radioactive material such as **iodine-131 (^{131}I)** can be released into the environment following nuclear reactor accidents, breach-of-containment at waste disposal sites, or atomic bomb blasts. Like non-radioactive iodine, ^{131}I is preferentially taken up and concentrated within the **thyroid gland**. There it can cause significant tissue damage that may result in radiation-induced hypothyroidism and **thyroid carcinoma** (particularly in younger patients). In the event of a nuclear accident, **potassium iodide** is given prophylactically to protect the thyroid from excessive accumulation of radioactive ^{131}I.

Energy-dependent transport of inorganic iodide into the thyroid follicular cell (iodide trapping) is accomplished by the sodium-iodide symporter located on the basolateral membrane. Because this transporter takes up all isotopes of iodide (as well as other ions such as perchlorate and pertechnetate), high serum levels of nonradioactive iodide can **competitively inhibit** radioactive I^{131} from entering thyroid follicular cells. Large increases in serum iodide levels also inhibit iodine organification (Wolff-Chaikoff effect) and reduce thyroid hormone release.

(Choice A) Levothyroxine is a synthetic form of T4 used to treat hypothyroidism. High doses of levothyroxine suppress TSH, just as high amounts of natural T4 would. Because TSH stimulates iodine trapping, high doses of levothyroxine would ultimately reduce iodine uptake in the thyroid follicular cells.

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(Choice A) Levothyroxine is a synthetic form of T4 used to treat hypothyroidism. High doses of levothyroxine suppress TSH, just as high amounts of natural T4 would. Because TSH stimulates iodine trapping, high doses of levothyroxine would ultimately reduce iodine uptake in the thyroid follicular cells. However, this regulatory process requires several days to weeks to take effect.

(Choices C and D) Propranolol is used to reduce the adrenergic effects of thyrotoxicosis (eg, tachycardia, tremor). Prednisone is used to reduce lymphocyte-mediated inflammatory effects in Graves ophthalmopathy. However, neither propranolol nor prednisone affects the uptake of iodine in thyroid follicular cells.

(Choice E) Propylthiouracil is used in the treatment of hyperthyroidism and decreases formation of thyroid hormone by inhibiting the enzyme thyroid peroxidase. Although inhibition of iodine organification will cause decreased iodide uptake by the thyroid, potassium iodide promotes this effect more rapidly and efficiently by also acting as a competitive inhibitor for iodide entry into the cell.

Educational objective:
Potassium iodide competitively inhibits thyroid uptake of radioactive iodine isotopes and is often administered following nuclear accidents to protect the thyroid and prevent development of radiation-induced thyroid carcinoma.

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A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight loss. She is referred for mammography, which reveals a 3-cm dominant mass in the left breast. Biopsy confirms the mass to be adenocarcinoma, and subsequent studies find that the tumor is estrogen receptor-positive and human epidermal growth factor receptor 2- (HER2) negative. The patient experienced menopause at age 52, and her past medical history is otherwise unremarkable. Anastrozole treatment is initiated and leads to a substantial decrease in the size of the primary tumor. Which of the following is the best explanation for the therapeutic effect of this agent?

A. Decreased androgen aromatization
B. Decreased androgen synthesis
C. Decreased follicular cell stimulation
D. Impaired ligand-receptor interaction
E. Impaired second-messenger action

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A 57-year-old woman comes to the office due to left breast pain associated with fatigue, nausea, and unexplained weight loss. She is referred for mammography, which reveals a 3-cm dominant mass in the left breast. Biopsy confirms the mass to be adenocarcinoma, and subsequent studies find that the tumor is estrogen receptor-positive and human epidermal growth factor receptor 2- (HER2) negative. The patient experienced menopause at age 52, and her past medical history is otherwise unremarkable. Anastrozole treatment is initiated and leads to a substantial decrease in the size of the primary tumor. Which of the following is the best explanation for the therapeutic effect of this agent?

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- A. Decreased androgen aromatization (70%)
- B. Decreased androgen synthesis (9%)
- C. ~~Decreased follicular cell stimulation~~ (3%)
- D. ~~Impaired ligand-receptor interaction~~ (14%)
- E. ~~Impaired second-messenger action~~ (2%)

70% 02 mins, 11 secs 08/10/2020

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Estrogens are synthesized primarily by the aromatization of androgens. **Aromatase** belongs to the P450 superfamily and is highly expressed in **ovarian tissue** (in which expression is **gonadotropin dependent**). Aromatase is also expressed in the adrenal cortex, subcutaneous fat, and breast. In the postmenopausal state, follicular atresia leads to reduced numbers of granulosa cells and decreased ovarian estrogen synthesis. However, the ovaries and adrenal glands continue to produce androgens in significant quantities, and **extraovarian aromatase** maintains a low level of estrogen in the peripheral circulation.

Estrogen is the main hormone driving the growth and development of estrogen receptor (ER)-positive malignant breast tumors. **Aromatase inhibitors** (eg, anastrozole, letrozole, exemestane) reduce the synthesis of estrogen from androgens, suppressing estrogen levels in postmenopausal women and **slowing progression of ER-positive tumors**. They are less effective as monotherapy in premenopausal women, as ovarian aromatase is upregulated substantially in response to gonadotropins.

(Choice B) Although inhibition of androgen synthesis could theoretically decrease estrogen synthesis, most androgen synthesis inhibitors (eg, ketoconazole) are nonspecific and suppress other pathways of steroidogenesis (eg, cortisol, mineralocorticoid).

(Choice C) Pulsatile stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) increases secretion of LH and FSH. However, continuous GnRH stimulation by long-acting GnRH analogs (eg,

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(Choice C) Pulsatile stimulation of the pituitary by gonadotropin-releasing hormone (GnRH) increases secretion of LH and FSH. However, continuous GnRH stimulation by long-acting GnRH analogs (eg, goserelin) suppresses LH and FSH release, decreasing production of estrogens in the ovarian follicle. These agents are useful for ovarian suppression in premenopausal women with ER-positive breast cancer.

(Choice D) Tamoxifen acts as either an antagonist or a partial agonist of the estrogen receptor, depending on the tissue. In breast tissue, tamoxifen antagonizes the estrogen receptor and can be used as adjuvant therapy for ER-positive breast cancer.

(Choice E) Many breast cancers overexpress epidermal growth factor receptor 2 (HER2). Trastuzumab is a monoclonal antibody against HER2 that is used in patients with HER2-positive tumors. It inhibits MAPK and PI3K/Akt signaling pathways, increases degradation of HER2, and facilitates antibody-mediated destruction of tumor cells.

Educational objective:
Estrogen is the main hormone responsible for the growth and development of estrogen receptor (ER)-positive breast tumors. Aromatase inhibitors (eg, anastrozole, letrozole, exemestane) decrease the synthesis of estrogen from androgens, suppressing estrogen levels and slowing progression of ER-positive tumors.

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A 32-year-old woman comes to the office due to neck swelling. The patient says her neck has gradually gotten larger, and she does not like how it appears in the mirror. She otherwise feels well and has no hoarseness, trouble swallowing, or shortness of breath. There is no history of head and neck irradiation. The patient has no prior medical conditions and takes no medications. She has a sister with vitiligo. Blood pressure is 110/60 mm Hg and pulse is 75/min. On physical examination, the thyroid is diffusely enlarged with no palpable nodules. There is no tracheal deviation. Serum TSH and free thyroxine levels are normal. Antibodies against thyroid peroxidase are present in high titers. The antigenic target of these antibodies is involved in which of the following processes?

A. Iodide uptake
B. Iodotyrosine deiodination
C. Thyroglobulin iodination
D. Thyroglobulin synthesis
E. Thyroxine to triiodothyronine conversion

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gotten larger, and she does not like how it appears in the mirror. She otherwise feels well and has no hoarseness, trouble swallowing, or shortness of breath. There is no history of head and neck irradiation. The patient has no prior medical conditions and takes no medications. She has a sister with vitiligo. Blood pressure is 110/60 mm Hg and pulse is 75/min. On physical examination, the thyroid is diffusely enlarged with no palpable nodules. There is no tracheal deviation. Serum TSH and free thyroxine levels are normal. Antibodies against thyroid peroxidase are present in high titers. The antigenic target of these antibodies is involved in which of the following processes?

A. ~~Iodide uptake~~ (4%)

B. ~~Iodotyrosine deiodination~~ (5%)

C. Thyroglobulin iodination (69%)

D. Thyroglobulin synthesis (8%)

E. ~~Thyroxine to triiodothyronine conversion~~ (11%)

Correct

69%

01 min, 20 secs

09/06/2020

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Thyroid follicular cells take up iodide (I^-), which is then transported into the thyroid follicular lumen, where it is oxidized to iodine (I_2). Following oxidation, in a process referred to as organification, iodine reacts with tyrosine residues in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodination). While still attached to thyroglobulin, DIT and MIT participate in 2 coupling reactions: The coupling of 2 DITs results in formation of **thyroxine** (T4); the combination of 1 DIT and 1 MIT leads to the formation of **triiodothyronine** (T3). Subsequently, thyroglobulin, which is now attached to multiple iodinated tyrosine compounds (ie, MIT, DIT, T3, T4), is engulfed by the thyroid follicular cells and digested within lysosomes, releasing T3 and T4 into the circulation. Free DIT and MIT are also produced, but only small amounts are secreted because iodotyrosine deiodinase removes the iodine groups from MIT and DIT for recycling **(Choice B)**.

Thyroid peroxidase (TPO) is a multifunctional enzyme that catalyzes the oxidation of iodide, the iodination of thyroglobulin, and the coupling reaction between 2 iodized tyrosine residues. Antibodies against TPO can be seen in a variety of autoimmune thyroid disorders, most commonly chronic lymphocytic (Hashimoto) thyroiditis (90% of patients). Hashimoto thyroiditis is a common cause of diffuse goiter, as in this patient. Although most patients develop residual hypothyroidism (low T4, elevated TSH), early in the disease they

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can be seen in a variety of autoimmune thyroid disorders, most commonly chronic lymphocytic (Hashimoto) thyroiditis (90% of patients). Hashimoto thyroiditis is a common cause of diffuse goiter, as in this patient. Although most patients develop residual hypothyroidism (low T4, elevated TSH), early in the disease they may be euthyroid (normal T4, normal TSH) or briefly hyperthyroid (elevated T4, suppressed TSH).

(Choice A) Uptake of iodide from the blood against its concentration gradient is an energy-dependent process carried out by the sodium-iodide symporter and stimulated by TSH. TPO is not involved in iodide uptake.

(Choice D) Thyroglobulin is a high-molecular-weight, glycosylated protein that is the major component of colloid in the thyroid follicle. TPO is involved in iodination, but not synthesis of thyroglobulin.

(Choice E) As noted above, the thyroid produces both T3 and T4, although most is in the form of T4. T3, the more active form of thyroid hormone, is produced primarily in peripheral tissues by deiodination of T4. This reaction is catalyzed by iodothyronine deiodinase, not by TPO.

Educational objective:
Thyroid peroxidase (TPO) catalyzes the oxidation of iodide to iodine, the iodination of thyroglobulin tyrosine residues, and the iodotyrosine coupling reaction that forms T3 and T4. Antibodies against TPO are present in >90% of patients with chronic lymphocytic (Hashimoto) thyroiditis.

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A 25-year-old woman comes to the office due to excessive facial hair growth that has worsened over the past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

A. Blockade of ornithine decarboxylase
B. Decreased androgen production
C. Increased insulin sensitivity
D. Inhibition of 5-α-reductase
E. Inhibition of androgen receptors

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past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

A. ~~Blockade of ornithine decarboxylase~~ (0%)

✓ B. Decreased androgen production (80%)

C. ~~Increased insulin sensitivity~~ (1%)

D. ~~Inhibition of 5-α-reductase~~ (6%)

E. ~~Inhibition of androgen receptors~~ (10%)

80% 31 secs 09/19/2020

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Excessive male-pattern hair growth in a woman is called **hirsutism**. Hirsutism can be due to increased androgen production (eg, polycystic ovary syndrome, Cushing syndrome, ovarian and adrenal tumors), increased local conversion of testosterone to dihydrotestosterone (DHT), or higher sensitivity of hair follicles to DHT (eg, idiopathic hirsutism). With excessive androgen exposure, soft, non-pigmented villous hair changes to coarse pigmented terminal hair in androgen-dependent areas of the body (eg, face, chest, back). **Virilization** occurs with very high androgen levels and is characterized by clitoromegaly, increased muscularity, and voice deepening in addition to hirsutism.

The most common cause of hirsutism is **polycystic ovary syndrome** (PCOS), which is often associated with elevated androgen levels. Combination oral contraceptive pills (OCPs) are usually the first choice for treating hirsutism in PCOS. OCPs work by suppressing LH secretion from the pituitary, thereby decreasing ovarian androgen production. They also increase sex hormone-binding globulin synthesis by the liver, decreasing free testosterone levels.

(Choice A) Ornithine decarboxylase is involved in DNA stabilization and repair. Inhibition leads to decreased cell growth and increased apoptosis. Eflornithine is a topical ornithine decarboxylase inhibitor used to decrease the rate of facial hair growth.

(Choice C) Patients with PCOS who develop diabetes mellitus are usually treated with metformin, which

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(Choice A) Ornithine decarboxylase is involved in DNA stabilization and repair. Inhibition leads to decreased cell growth and increased apoptosis. Eflornithine is a topical ornithine decarboxylase inhibitor used to decrease the rate of facial hair growth.

(Choice C) Patients with PCOS who develop diabetes mellitus are usually treated with metformin, which increases insulin sensitivity. Metformin can also help normalize menses but would not improve hirsutism.

(Choices D and E) Testosterone receptor antagonists (eg, spironolactone) are effective in suppressing androgen-dependent hair growth. 5-α-reductase inhibitors (eg, finasteride) decrease peripheral conversion of testosterone to DHT but are less effective than testosterone receptor antagonists in treating hirsutism. Both are strongly teratogenic.

Educational objective:
Male-pattern hair growth in a woman is called hirsutism; the most common cause is polycystic ovary syndrome. Combination oral contraceptive pills can treat hirsutism by suppressing pituitary LH secretion and subsequently decreasing ovarian androgen production.

References

- Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline

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www.ncbi.nlm.nih.gov/pubmed/18252793

A 48-year-old man with type 2 diabetes mellitus comes to the office for a follow-up appointment. The patient was diagnosed 4 years ago and was initially managed with metformin, but that medication had to be discontinued due to diarrhea. He is currently being treated with the maximum therapeutic dose of glipizide, but has persistently elevated blood glucose levels. Laboratory results show a fasting blood glucose of 180 mg/dL and hemoglobin A1c of 8.6%. The patient does not want to take insulin or other injectable diabetic medications. After discussing various treatment options, canagliflozin is added to his current regimen. Which of the following tests should be ordered prior to initiating the new therapy in this patient?

A. Leukocyte count
B. Serum creatinine
C. Serum uric acid
D. Thyroid function tests
E. Urinalysis

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A. Leukocyte count (4%)
B. Serum creatinine (66%)
C. Serum uric acid (4%)
D. ~~Thyroid function tests~~ (3%)
E. Urinalysis (21%)

66%
51 secs
09/12/2020

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Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal tubule. **SGLT2 inhibitors** (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that **decrease renal reabsorption of glucose**, leading to increased urinary glucose loss and decreased blood glucose levels. They are primarily used in patients who do not tolerate or have inadequate diabetic control with first-line medications (eg, metformin).

The **effectiveness** of SGLT2 inhibitors is **dependent on glomerular filtration** of glucose, which is decreased in patients with chronic kidney disease. For this reason, an estimate of glomerular filtration with **serum creatinine** is recommended prior to initiation of therapy and periodically thereafter. Side effects include **genitourinary tract infections** due to glucosuria and moderate osmotic diuresis that can cause **symptomatic hypotension** (particularly in elderly individuals and patients taking diuretics).

(Choice A) A leukocyte count is not required before initiating treatment with antidiabetic agents.

(Choice C) Certain drugs such as diuretics (eg, thiazide, loop) and antituberculosis drugs (eg, pyrazinamide, ethambutol) reduce uric acid clearance and may precipitate gout. However, SGLT2 inhibitors are associated with increased uric acid excretion.

(Choice D) Thyroid function tests are routinely performed on patients taking lithium and amiodarone as these drugs can alter thryoid hormone metabolism. However, thyroid function tests are not required for

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(Choice D) Thyroid function tests are routinely performed on patients taking lithium and amiodarone as these drugs can alter thryoid hormone metabolism. However, thyroid function tests are not required for antidiabetic medications.

(Choice E) Although SGLT2 inhibitors increase the risk of urinary tract infections, urinalysis prior to initiating therapy would not be of use.

Educational objective:
Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. In patients with chronic kidney disease, these medications are less effective. Therefore, serum creatinine should be measured prior to therapy.

References

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Sodium-glucose cotransporter 2 inhibitors (eg, canagliflozin, dapagliflozin) decrease renal reabsorption of glucose, leading to urinary glucose loss and decreased blood glucose levels. In patients with chronic kidney disease, these medications are less effective. Therefore, serum creatinine should be measured prior to therapy.

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A 32-year-old man comes to the office due to vision problems. Over the last 6 weeks, he has had several "near-misses" while driving, having been nearly hit by cars coming from both the right and left sides. He also reports frequent headaches. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals deficits in the bilateral temporal visual fields. Extraocular movements are bilaterally intact, and the remainder of the neurological examination shows no abnormalities. Which of the following additional findings is most likely to be present in this patient?

A. Decreased libido
B. Enlarged jaw bone
C. Excessive urination
D. Heat intolerance
E. Skin hyperpigmentation
F. Skin thinning

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- A. Decreased libido (81%)
- B. Enlarged jaw bone (5%)
- C. Excessive urination (3%)
- D. Heat intolerance (2%)
- E. Skin hyperpigmentation (4%)
- F. Skin thinning (1%)

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Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) Mass effect

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(LH, FSH)	• Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can cause **bitemporal hemianopsia**. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

(Choices B, D, and F) Somatotroph (growth hormone-secreting) adenomas can present with gigantism (in children) or acromegaly in adults. Thyrotroph (TSH-secreting) adenomas cause central hyperthyroidism (eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a

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(eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a characteristic feature of Cushing syndrome; when hypercortisolism is due to a corticotroph (ACTH-producing) adenoma, it is referred to as Cushing disease. These tumors are significantly less common than prolactinomas.

(Choice C) Mass lesions involving the pituitary stalk or posterior pituitary could cause headaches and bitemporal hemianopsia in addition to central diabetes insipidus (due to decreased release of antidiuretic hormone [ADH] from the posterior pituitary). However, polyuria is typically only transient (lasting <6 weeks) because the hypothalamus is able to bypass the pituitary and directly release ADH into the circulation.

(Choice E) Hyperpigmentation in the context of pituitary disease is typically due to hypersecretion of ACTH, either due to a corticotroph adenoma or in response to primary adrenal insufficiency.

Educational objective:
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can cause galactorrhea and amenorrhea in women. In men, they often present with hypogonadism.

References

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A 1-week-old newborn is seen for abnormal thyroid function tests that were performed as part of routine screening. Serum thyroxine (T4) was low and serum TSH was normal. The patient was born by spontaneous vaginal delivery at 40 weeks of gestation to a 28-year-old primigravida. During the pregnancy, the mother took acetaminophen intermittently for low back pain. Examination of the newborn shows no abnormal findings. Repeat thyroid function test results are as follows:

Free T4	1.2 µg/dL (normal: 0.8-1.95)
Total T4	4 µg/dL
TSH	3 µU/mL

Which of the following is the most likely cause of the patient's abnormal thyroid function tests?

A. Decreased T4 to triiodothyronine conversion
B. Deficiency of thyroxine-binding globulin
C. Hypoalbuminemia
D. Hypopituitarism

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Which of the following is the most likely cause of the patient's abnormal thyroid function tests?

A. Decreased T4 to triiodothyronine conversion
B. Deficiency of thyroxine-binding globulin
C. Hypoalbuminemia
D. Hypopituitarism
E. Thyroid dysgenesis

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www.ncbi.nlm.nih.gov/pubmed/18252793

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pregnancy, the mother took acetaminophen intermittently for low back pain. Examination of the newborn shows no abnormal findings. Repeat thyroid function test results are as follows:

Free T4	1.2 µg/dL (normal: 0.8-1.95)
Total T4	4 µg/dL
TSH	3 µU/mL

Which of the following is the most likely cause of the patient's abnormal thyroid function tests?

A. Decreased T4 to triiodothyronine conversion (10%)
B. Deficiency of thyroxine-binding globulin (59%)
C. ~~Hypoalbuminemia~~ (8%)
D. ~~Hypopituitarism~~ (4%)
E. ~~Thyroid dysgenesis~~ (18%)

Correct

59%

02 mins, 07 secs

09/18/2020

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www.ncbi.nlm.nih.gov/pubmed/18252793

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This neonate with a low total thyroxine (T4) but normal free T4 and normal TSH likely has a **deficiency** of **thyroxine-binding globulin** (TBG). Congenital TBG deficiency is a **benign**, X-linked disorder usually identified on newborn screening.

In general, the majority of circulating T4 is bound to TBG, which then serves as a storage pool to replenish the biologically active free T4 that is continuously cleared by the kidneys. Therefore, TBG helps **maintain a constant free T4 level**.

When TBG is deficient, less T4 is bound and a greater proportion is allowed to freely circulate. **Total T4 is low** due to the decrease in bound T4 fraction. However, since physiologic feedback is intact, **TSH and free T4 levels remain normal**. Because the levels of active (free) thyroid hormone are normal, patients are clinically **euthyroid** and asymptomatic, so **no treatment** is required.

(Choice A) Certain placentally transferred maternal medications (eg, propylthiouracil) decrease conversion of T4 to triiodothyronine (T3), causing transient neonatal hypothyroidism (ie, low T4, high TSH). Acetaminophen does not interfere with thyroid hormone synthesis.

(Choice C) Because only a small percentage of T4 is bound to albumin, hypoalbuminia does not

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Acetaminophen does not interfere with thyroid hormone synthesis.

(Choice C) Because only a small percentage of T4 is bound to albumin, hypoalbuminia does not significantly affect thyroid hormone levels. In addition, this patient has no risk factors for hypoalbuminemia (eg, malnutrition, sepsis, gastrointestinal/renal loss).

(Choice D) Hypopituitarism causes central hypothyroidism, which is characterized by low TSH, total T4, and free T4. Other midline defects (eg, cleft lip) or hormonal imbalances (eg, hypoglycemia due to ACTH deficiency) are often present.

(Choice E) Thyroid dysgenesis (eg, ectopy, hypoplasia) is the most common cause of congenital hypothyroidism, which is usually asymptomatic at birth. In contrast to this case, laboratory findings include high TSH and low total and free T4.

Educational objective:

Thyroxine-binding globulin deficiency is a benign disorder characterized by low total thyroxine (T4) and normal free T4 and TSH levels. Patients are euthyroid and do not require treatment.

References

- Inherited defects in thyroxine binding globulins.

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www.ncbi.nlm.nih.gov/pubmed/26522458

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A 21-year-old man undergoes a routine pre-employment physical examination. During testicular examination, he is found to have only 1 testis in his scrotum. Further evaluation reveals an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is likely to be impaired in this patient?

A. Testosterone
B. Dihydrotestosterone
C. DHEA
D. Inhibin B
E. Cortisol

Submit

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A 21-year-old man undergoes a routine pre-employment physical examination. During testicular examination, he is found to have only 1 testis in his scrotum. Further evaluation reveals an elevated serum FSH level and a normal serum LH level. Production of which of the following substances is likely to be impaired in this patient?

A. Testosterone (10%)
B. Dihydrotestosterone (6%)
C. DHEA (3%)
✓ D. Inhibin B (78%)
E. Cortisol (0%)

Correct

78% Answered correctly

26 secs Time Spent

11/23/2020 Last Updated

Explanation

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Pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both FSH and LH are produced by the gonadotroph cells of the anterior pituitary. LH stimulates the release of testosterone from the Leydig cells of the testes; FSH stimulates the release of inhibin B from the Sertoli cells of the testes. Testosterone has a negative feedback effect on LH and GnRH secretion, and inhibin B suppresses FSH secretion.

Sertoli cells are present within the seminiferous tubules of the testes. In patients with 1 testicle, the mass of Sertoli cells is significantly reduced. Therefore, the circulating levels of inhibin B are likely to be low in these patients. Low inhibin B levels will not provide adequate negative feedback on FSH secretion, thus FSH levels will tend to be elevated in males who only have 1 testicle.

A male patient of any age who has only 1 testicle requires further evaluation. Since there is an increased cancer risk in men with an undescended testicle, most of these “abdominal testicles” are either removed (orchiectomy) or receive surgery that allows descent into the scrotum (orchiopexy).

(Choices A, B, and C) Although the number of Leydig cells is reduced when only 1 testicle is present, androgen levels are not affected due to compensation by the remaining Leydig cell mass. Additionally, this

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(Choices A, B, and C) Although the number of Leydig cells is reduced when only 1 testicle is present, androgen levels are not affected due to compensation by the remaining Leydig cell mass. Additionally, this patient has a normal LH level, indicating that there is adequate androgenic feedback to the hypothalamus and pituitary. Testosterone, dihydrotestosterone, and DHEA cause LH feedback inhibition, but they are not part of the FSH feedback loop.

(Choice E) Cortisol has no direct relationship with LH and FSH secretion. High circulatory levels of cortisol, however, do produce hypogonadotropic hypogonadism by suppressing the release of gonadotrophin-releasing hormone.

Educational objective:
Inhibin B is produced by the Sertoli cells and is the physiological inhibitor of FSH secretion. LH concentration is controlled primarily by testosterone feedback.

Physiology	Endocrine, Diabetes & Metabolism	Cryptorchidism
Subject	System	Topic

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A 34-year-old woman experiences nausea, abdominal pain, and dizziness after undergoing open reduction and internal fixation of a femur fracture. One year ago, she was diagnosed with systemic lupus erythematosus with significant renal involvement, and she has since been on chronic glucocorticoid therapy with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

	Corticotropin-releasing hormone	ACTH	Cortisol
A.	Increased	Increased	Increased
B.	Increased	Increased	Decreased
C.	Increased	Decreased	Decreased
D.	Decreased	Decreased	Increased
E.	Decreased	Decreased	Decreased

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with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

	Corticotropin-releasing hormone	ACTH	Cortisol	
A.	~~Increased~~	~~Increased~~	~~Increased~~	(1%)
B.	~~Increased~~	~~Increased~~	~~Decreased~~	(12%)
C.	Increased	Decreased	Decreased	(6%)
D.	~~Decreased~~	~~Decreased~~	~~Increased~~	(22%)
✓ E.	Decreased	Decreased	Decreased	(56%)

Correct

56%

01 min, 13 secs

01/12/2021

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This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus and also block its ACTH stimulatory effect on the anterior pituitary. Long-term suppression leads to **atrophy** of hypothalamic CRH-releasing neurons, pituitary corticotrophic cells, and the adrenal zona reticularis (androgen- producing inner zone) and zona fasciculata (cortisol-producing middle zone).

Chronic glucocorticoid use is characterized by **low** CRH, ACTH, and cortisol levels that **cannot rise** in response to stressful situations (eg, infections, surgery) **(Choice A)**. This lack of a stress response can result in **relative glucocorticoid deficiency** even when the patient's baseline glucocorticoid regimen is maintained. Because glucocorticoids help maintain normal vascular tone (eg, by increasing norepinephrine, renin, and angiotensin vasoconstrictive activity), glucocorticoid deficiency can precipitate **hypotension/shock**. In such cases, a higher **stress dose** is needed to compensate for the increased physiologic demands and prevent the development of adrenal crisis.

(Choice B) Increased levels of CRH and ACTH with decreased cortisol suggest primary adrenal insufficiency, as may be seen in autoimmune adrenalitis or bilateral adrenal hemorrhage/infarction. These patients will also have mineralocorticoid deficiency and are at very high risk for adrenal crisis.

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physiologic demands and prevent the development of adrenal crisis.

(Choice B) Increased levels of CRH and ACTH with decreased cortisol suggest primary adrenal insufficiency, as may be seen in autoimmune adrenalitis or bilateral adrenal hemorrhage/infarction. These patients will also have mineralocorticoid deficiency and are at very high risk for adrenal crisis.

(Choice C) Increased CRH with decreased levels of ACTH and cortisol suggest a pituitary disorder. ACTH is secreted by corticotroph cells of the anterior pituitary; damage to the pituitary by a tumor, infarction, or infection can cause decreased release of ACTH, which in turn leads to decreased cortisol production.

(Choice D) Excessive cortisol production from an autonomous adrenal adenoma suppresses CRH and ACTH production by the hypothalamus and pituitary, respectively.

Educational objective:
Suppression of the hypothalamus-pituitary-adrenal axis by glucocorticoid therapy is the most common cause of adrenal insufficiency. In these patients, adrenal crisis can be precipitated by stressful situations (eg, infections, surgery) if the glucocorticoid dose is not increased appropriately.

References

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STEP1 QBank

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Previous Tests

Show: Columns

Search

SCORE	NAME	DATE	MODE	Q.POOL	SUBJECTS	SYSTEMS	# QS	ACTIONS
	14	Feb 13, 2021	Tutor	Unused	All	Gastrointestinal ...	40	
	13	Feb 12, 2021	Tutor	Unused	All	Gastrointestinal ...	40	
88%	12	Feb 11, 2021	Tutor	Unused	All	Gastrointestinal ...	40	
	11	Feb 11, 2021	Tutor	Unused	All	Gastrointestinal ...	40	
88%	10	Feb 10, 2021	Tutor	Unused	All	Gastrointestinal ...	40	
	9	Feb 10,	Tutor	Unused	All	Gastrointestinal ...	40	

A 7-year-old boy is brought to the clinic for a well-child visit. Over the past year, the patient has become fidgety, impulsive, inattentive, and restless, leading to a progressive decline in his grades. Height and weight are at the 50th and 5th percentiles for his age, respectively. The patient takes no medications or supplements. The thyroid gland is diffusely enlarged to palpation without tenderness or bruit. Neurologic examination reveals no focal findings. Results of thyroid function tests are as follows:

TSH	7 mU/L
Thyroxine, total	16 µg/dL
Triiodothyronine	210 ng/dL (normal: 80-195)

Which of the following is the most likely etiology of this patient's thyroid function test abnormalities?

A. Chronic autoimmune thyroiditis
B. Elevated thyroxine-binding globulin
C. Graves disease
D. Organification defect in thyroid hormone synthesis

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fidgety, impulsive, inattentive, and restless, leading to a progressive decline in his grades. Height and weight are at the 50th and 5th percentiles for his age, respectively. The patient takes no medications or supplements. The thyroid gland is diffusely enlarged to palpation without tenderness or bruit. Neurologic examination reveals no focal findings. Results of thyroid function tests are as follows:

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Which of the following is the most likely etiology of this patient's thyroid function test abnormalities?

A. Chronic autoimmune thyroiditis
B. Elevated thyroxine-binding globulin
C. Graves disease
D. Organification defect in thyroid hormone synthesis
E. Resistance to thyroid hormone

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supplements. The thyroid gland is diffusely enlarged to palpation without tenderness or bruit. Neurologic examination reveals no focal findings. Results of thyroid function tests are as follows:

TSH	7 mU/L
Thyroxine, total	16 µg/dL
Triiodothyronine	210 ng/dL (normal: 80-195)

Which of the following is the most likely etiology of this patient's thyroid function test abnormalities?

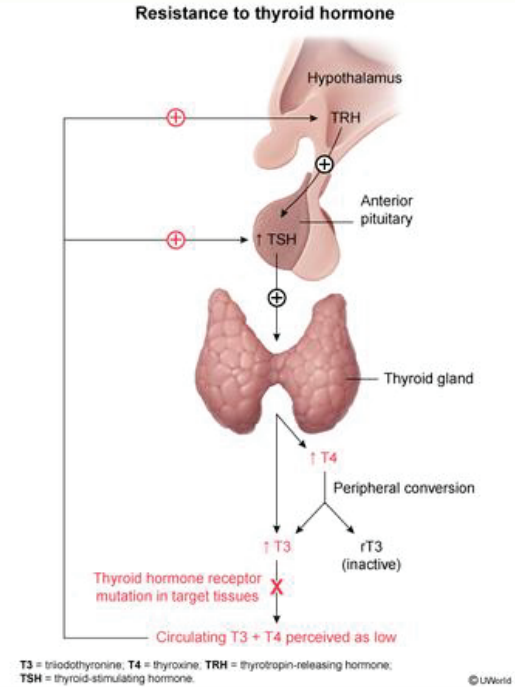
A. Chronic autoimmune thyroiditis (11%)
B. Elevated thyroxine-binding globulin (15%)
C. Graves disease (22%)
D. Organification defect in thyroid hormone synthesis (7%)
✓ E. Resistance to thyroid hormone (43%)

Correct
43%
51 secs
09/18/2020

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This patient's **increased** levels of **thyroxine (T4)**, **triiodothyronine (T3)**, and **TSH** are concerning for **thyroid hormone resistance**. Most cases are due to an inherited mutation affecting **thyroid hormone receptor beta**, which results in **decreased thyroid hormone sensitivity** in the hypothalamic-pituitary-thyroid axis and peripheral tissues. Increased levels of T3 and T4 normally provide negative feedback to the pituitary to decrease TSH production. However, because pituitary cells are also resistant to thyroid hormone in this condition, TSH rises, driving further production of T3 and T4.

The presentation of thyroid hormone resistance varies greatly due to fluctuating thyroid hormone sensitivity in different target tissues; patients may be asymptomatic (ie, euthyroid) or develop hypothyroid or hyperthyroid symptoms (eg, low weight, as in this patient). The most common finding is **goiter** due to overstimulation of the thyroid gland by TSH. **Attention deficit hyperactivity disorder** (ADHD) and **tachycardia** are also common due to the preponderance of alpha thyroid hormone receptors (with normal sensitivity) in the CNS and heart.

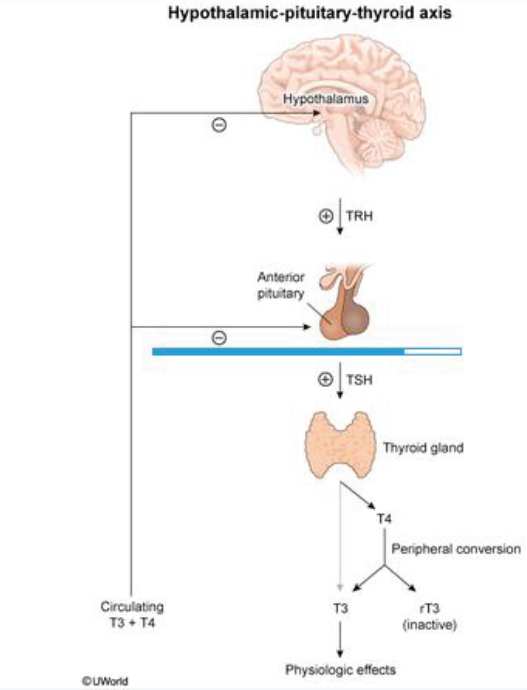
(Choice A) Chronic autoimmune (Hashimoto) thyroiditis leads to autoantibody-mediated thyroid gland destruction characterized by goiter and symptoms of hypothyroidism (eg, fatigue, constipation, dry skin). Low T3 and T4 production results in increased TSH.

(Choice B) Thyroxine-binding globulin (TBG) binds thyroid hormones and maintains a constant pool of free T3 and T4. Increases in TBG (eg, pregnancy) result in a clinically euthyroid, asymptomatic state

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This patient's **increased** levels of **thyroxine (T4)**, **triiodothyronine (T3)**, and **TSH** are concerning for

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free T3 and T4. Increases in TBG (eg, pregnancy) result in a clinically euthyroid, asymptomatic state

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Low T3 and T4 production results in increased TSH.

(Choice B) Thyroxine-binding globulin (TBG) binds thyroid hormones and maintains a constant pool of free T3 and T4. Increases in TBG (eg, pregnancy) result in a clinically euthyroid, asymptomatic state characterized by an increased total T3 and T4 but normal levels of free hormones and TSH.

(Choice C) TSH receptor–stimulating antibodies in Graves disease cause increased T3 and T4 production with signs of hyperthyroidism, including goiter. In contrast to this patient, those with this condition have appropriate negative feedback to the pituitary, leading to low TSH levels.

(Choice D) Defective thyroid hormone synthesis leads to overt hypothyroidism starting in infancy; symptoms include lethargy, hypotonia, and constipation. Laboratory evaluation shows low T3 and T4 and elevated TSH.

Educational objective:
Thyroid hormone resistance is characterized by decreased sensitivity of peripheral tissues to thyroid hormones due to a defect in the thyroid hormone receptor. Levels of thyroxine, triiodothyronine, and TSH are increased. Patients classically have goiter and frequently develop attention deficit hyperactivity disorder.

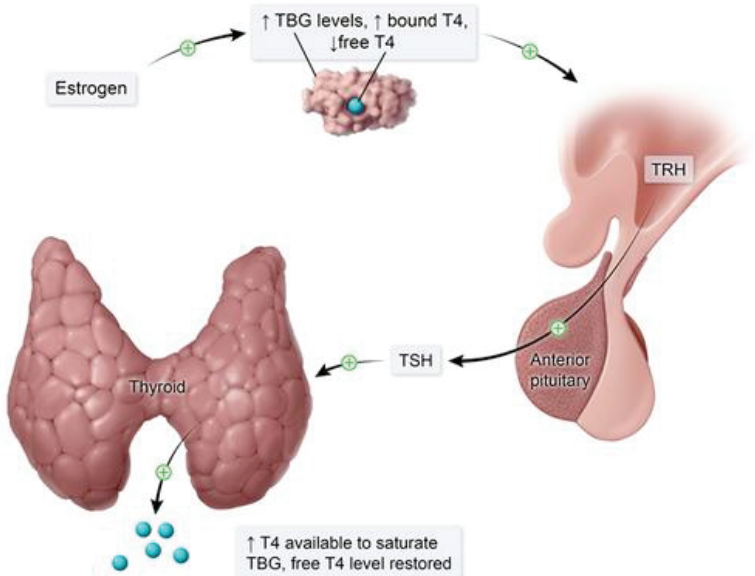
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Low T3 and T4 production results in increased TSH

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Estrogen effect on thyroid hormone production



TBG = thyroxine-binding globulin.

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A 29-year-old woman comes to the office due to unintentional weight loss, fatigue, and sweating. The patient has had no neck pain. Two months ago, she delivered a healthy boy with no perinatal complications. The patient does not breastfeed the infant. She has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination, including pelvic examination, is normal. Laboratory evaluation reveals low serum TSH, elevated serum thyroxine (T4), and elevated serum triiodothyronine (T3). Thyrotropin receptor antibodies are negative. Which of the following is the most likely cause of this patient's symptoms?

A. Exogenous intake of thyroid hormone
B. Granulomatous inflammation of the thyroid gland
C. Lymphocytic inflammation of the pituitary gland
D. Lymphocytic inflammation of the thyroid gland
E. Tumor production of β-hCG

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patient has had no neck pain. Two months ago, she delivered a healthy boy with no perinatal complications. The patient does not breastfeed the infant. She has no chronic medical conditions and takes no medications. Blood pressure is 140/70 mm Hg, pulse is 110/min, and respirations are 16/min. Oxygen saturation is 98% on room air. Neck examination shows mild, diffuse enlargement of the thyroid gland with no tenderness. The remainder of the physical examination, including pelvic examination, is normal. Laboratory evaluation reveals low serum TSH, elevated serum thyroxine (T4), and elevated serum triiodothyronine (T3). Thyrotropin receptor antibodies are negative. Which of the following is the most likely cause of this patient's symptoms?

A. ~~Exogenous intake of thyroid hormone~~ (14%)

B. Granulomatous inflammation of the thyroid gland (13%)

C. ~~Lymphocytic inflammation of the pituitary gland~~ (4%)

✓ D. Lymphocytic inflammation of the thyroid gland (53%)

E. ~~Tumor production of β-hCG~~ (14%)

53% 01 min, 27 secs 11/15/2020

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Postpartum thyroiditis	
Pathophysiology	• Autoimmune destruction of thyroid follicles & release of preformed thyroid hormone • Lymphocytic infiltrates ± germinal centers
Clinical course	• Onset ≤12 months after pregnancy • Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH) • Brief hypothyroid phase (↓ T4 & T3, ↑ TSH) • Return to euthyroid state
Diagnosis	• ↑ Serum thyroglobulin • ↓ Radioiodine uptake • Ultrasound: diffuse thyroid enlargement with ↓ blood flow

T3 = triiodothyronine; **T4** = thyroxine.

This patient has weight loss, tachycardia, and a painless, diffuse goiter; her serum thyroid hormone levels are elevated and TSH is suppressed, findings consistent with **primary hyperthyroidism**. In light of her

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This patient has weight loss, tachycardia, and a painless, diffuse goiter; her serum thyroid hormone levels are elevated and TSH is suppressed, findings consistent with **primary hyperthyroidism**. In light of her recent pregnancy and negative thyrotropin receptor antibody assay (which makes Graves disease unlikely) this is most likely due to **postpartum thyroiditis**.

Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by **autoimmune destruction of thyroid follicles** similar to that seen in chronic lymphocytic (Hashimoto) thyroiditis. Histologic inspection demonstrates **lymphocytic infiltration**, sometimes with the formation of germinal centers. The breakdown of follicle margins and loss of colloid may also be seen.

Postpartum thyroiditis typically begins with a hyperthyroid phase due to the **release of preformed thyroid hormone**, followed by a transient hypothyroid phase due to the depletion of thyroid hormone and an eventual return to a euthyroid state.

(Choice A) Intake of exogenous thyroid hormone can cause thyrotoxicosis with suppression of TSH. However, thyroid enlargement would not be seen (thyroid atrophy is more typical).

(Choice B) Like postpartum thyroiditis, subacute granulomatous (de Quervain/postviral) thyroiditis can have a transient hyperthyroid phase due to the release of preformed thyroid hormone. However, patients

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Differential diagnosis of thyroiditis

Painful thyroiditis	Painless thyroiditis	Graves	Fibrotic
Pain & tenderness Systemic symptoms	Autoimmune/+TPO antibody Destruction of follicles Release of preformed hormone & thyroglobulin	+TSI/TRAb ↑ Thyroid hormone synthesis	Replacement of follicles with fibrotic tissue
Subacute (granulomatous, DeQuervain) • Tender goiter • Transient hyperthyroid phase • Postviral syndrome **Acute** (suppurative) • Fever • Asymmetry • Fluctuance	**Chronic lymphocytic** (Hashimoto) • Common • Usually hypothyroid at diagnosis **Postpartum** • ≤12 months after parturition • Transient hyperthyroid phase	**Graves disease** • Overt hyperthyroidism • ↑ RAIU • Ophthalmopathy	**Riedel thyroiditis** • Hard/fixed goiter • Compression of esophagus & trachea

TPO = thyroid peroxidase; **TSI** = thyroid-stimulating immunoglobulin;
TRAb = thyrotropin receptor antibody; **RAIU** = radioiodine uptake.

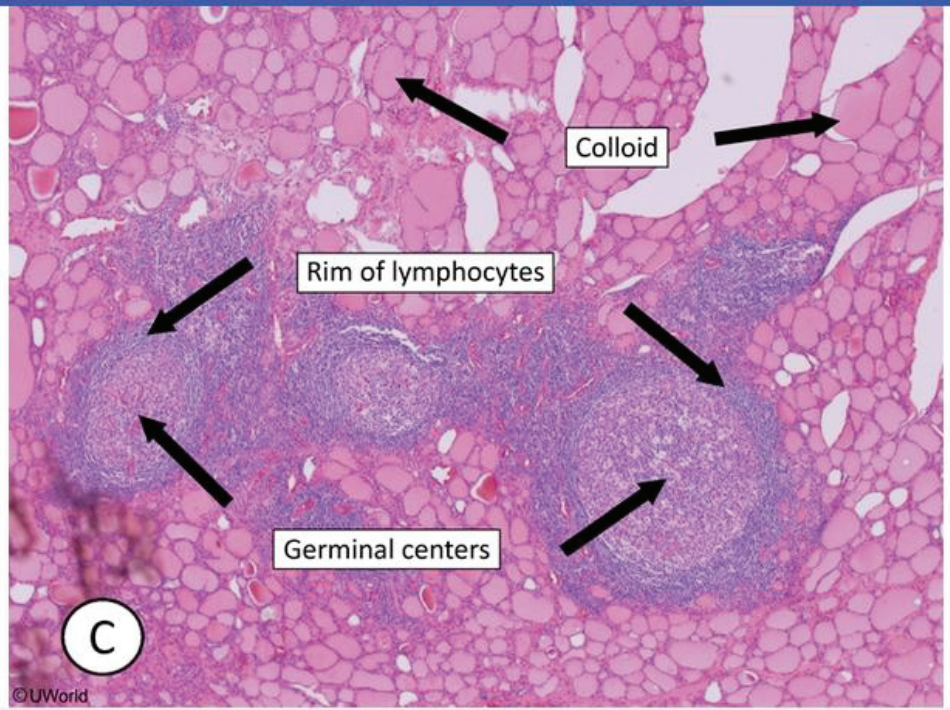
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have a transient hyperthyroid phase due to the release of preformed thyroid hormone. However, patients typically have low-grade fever, myalgias, and a painful, tender goiter.

(Choice C) Lymphocytic hypophysitis is an uncommon disorder that may occur in postpartum women. TSH would be low due to loss of pituitary thyrotrophs, but thyroid hormone levels would also be low (ie, central/secondary hypothyroidism).

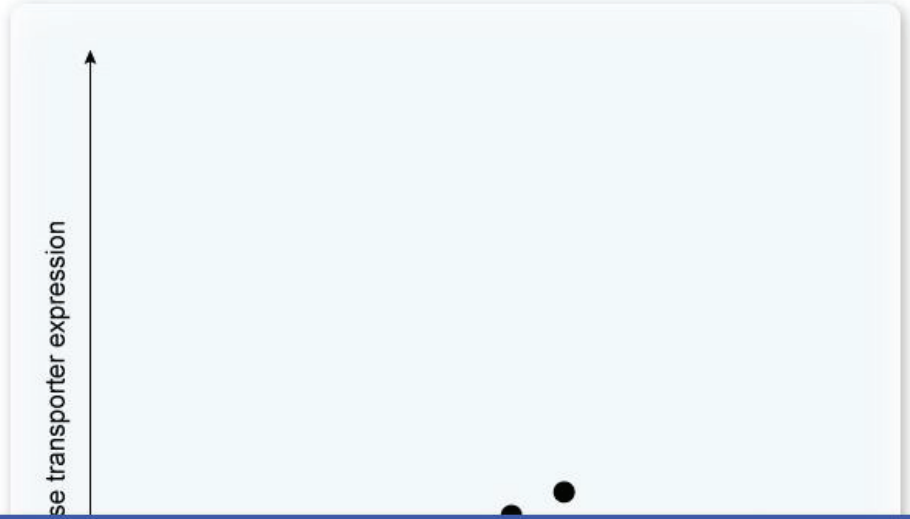
(Choice E) The beta subunit of hCG shares homology with TSH and can stimulate TSH receptors on follicular cells. Gestational trophoblastic neoplasia refers to a group of hCG-secreting tumors that most commonly occur in association with molar pregnancy (uncommon following live birth). Most patients have associated symptoms such as amenorrhea or abnormal uterine bleeding, and examination often shows uterine enlargement.

Educational objective:
Postpartum thyroiditis occurs within 12 months of pregnancy and is characterized by autoimmune destruction of thyroid follicles. It typically begins with a hyperthyroid phase due to the release of preformed thyroid hormone, followed by a hypothyroid phase due to depletion of thyroid hormone and an eventual return to a euthyroid state. Histologic inspection demonstrates lymphocytic infiltration with the formation of germinal centers, which is similar to chronic lymphocytic (Hashimoto) thyroiditis.

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Researchers are investigating the relationship between glucose transport proteins and insulin concentration in different types of tissues. Experiments in which cells are taken from various tissue samples and exposed to increasing concentrations of insulin are performed. The number of surface glucose transporters are then measured. The results from 2 cell samples are plotted on the graphs below.

Cell sample A

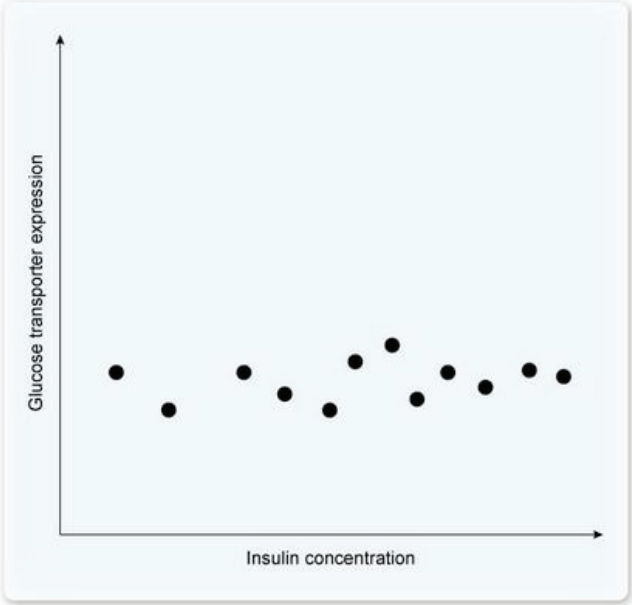


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Cell sample A



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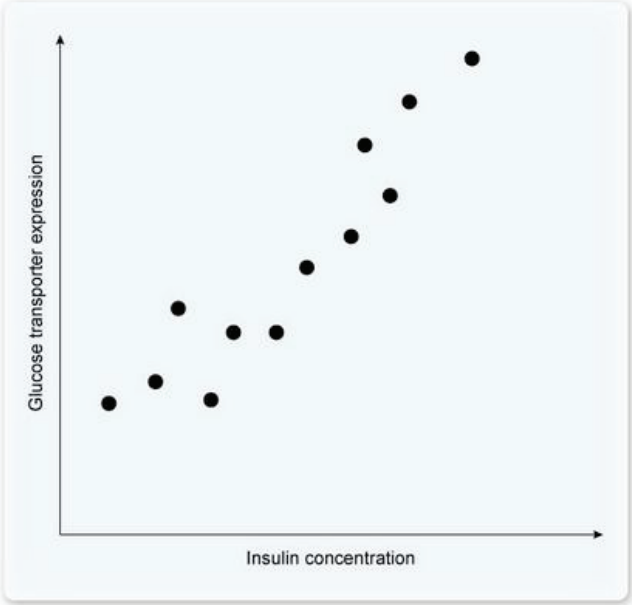
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Cell sample B



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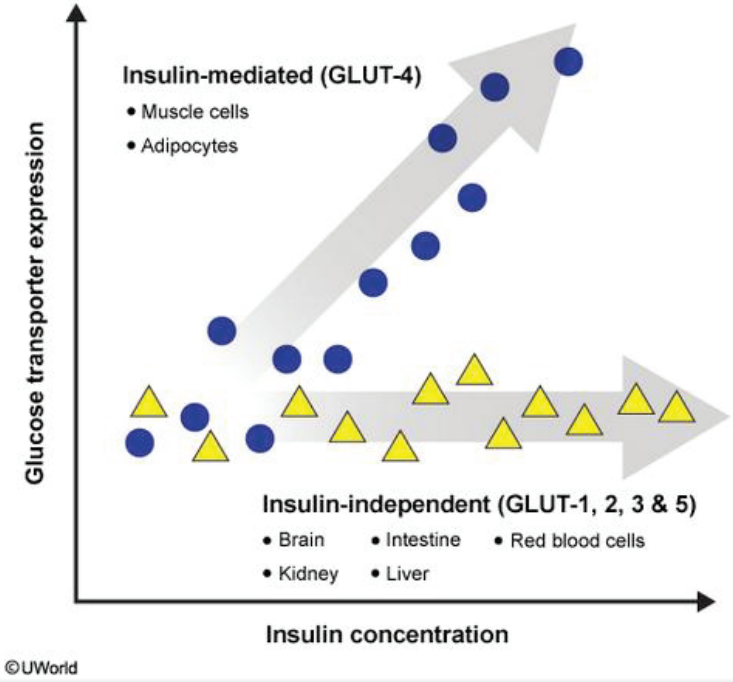
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Which of the following cell types are most likely represented in cell samples A and B, respectively?

	Cell sample A	Cell sample B	
A.	Cerebral neurons	Hepatocytes	(24%)
B.	Intestinal epithelial cells	Pancreatic beta cells	(5%)
C.	Renal tubular cells	Hepatocytes	(9%)
✓ D.	Renal tubular cells	Skeletal myocytes	(54%)
E.	Skeletal myocytes	Adipocytes	(6%)

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The **glucose transport proteins** (GLUTs) are a family of transmembrane proteins responsible for transport of glucose across cell membranes. Of these, only **GLUT-4** is **responsive to insulin**. In the absence of insulin, GLUT-4 is sequestered in the cytoplasm and the cells become less permeable to glucose. However, increasing insulin concentrations induce translocation of GLUT-4 to the plasma membrane, facilitating glucose transport into the cell (**sample B**). GLUT-4 is predominantly expressed in **skeletal muscle cells and adipocytes**, where it facilitates insulin-mediated glucose uptake and storage.

In contrast to GLUT-4, **GLUTs 1, 2, 3, and 5** are always present on the plasma membrane, regardless of insulin levels, and are responsible for **insulin-independent** glucose transport (**sample A**).

- GLUT-1 contributes to basal glucose transport in erythrocytes and at the blood-brain barrier.
- GLUT-2 is present in hepatocytes, pancreatic beta cells, and at the basolateral membrane of **renal tubules** and small intestinal mucosa. It plays a role in absorption of dietary glucose, reabsorption of glucose from renal tubules, hepatic glucose regulation, and sensitivity of beta cells to circulating glucose.
- GLUT-3 is involved in placental and neuronal glucose transport.
- GLUT-5 is a fructose transporter found in spermatocytes and the gastrointestinal tract.

(Choices A, B, and C) Glucose uptake by hepatocytes, pancreatic beta cells, neurons, and enterocytes

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- GLUT-3 is involved in placental and neuronal glucose transport.
- GLUT-5 is a fructose transporter found in spermatocytes and the gastrointestinal tract.

(Choices A, B, and C) Glucose uptake by hepatocytes, pancreatic beta cells, neurons, and enterocytes primarily involves insulin-independent glucose transporters and does not substantially change with insulin concentration.

(Choice E) Both skeletal myocytes and adipocytes express GLUT-4 and would show increased glucose uptake in response to insulin.

Educational objective:

Glucose transport protein (GLUT)-4 is an insulin-sensitive glucose transporter expressed in skeletal muscle cells and adipocytes that translocates to the plasma membrane in response to increasing insulin levels. In contrast, GLUT-1, 2, 3, and 5 are always present on the plasma membrane and constitutively transport glucose in an insulin-independent manner.

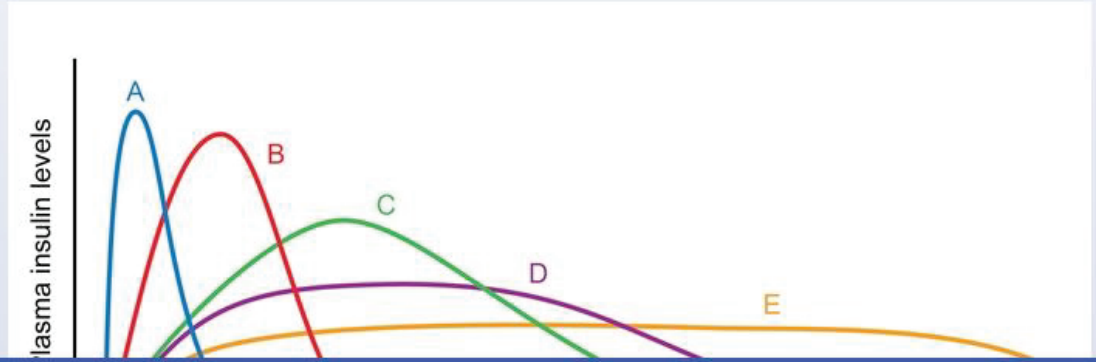
References

- Cellular regulation of glucose uptake by glucose transporter GLUT4.

Biochemistry Endocrine, Diabetes & Metabolism Diabetes mellitus

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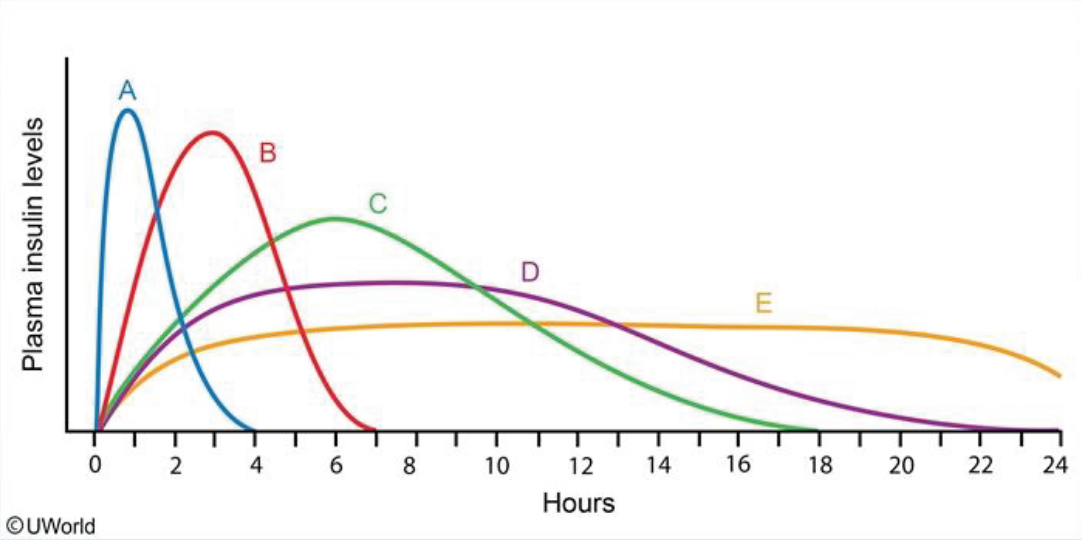
A 21-year-old man comes to the emergency department due to several days of dizziness and extreme fatigue. The patient has been drinking a lot of water and urinating more than usual for the past 2 weeks. He developed nausea and vomiting a day ago and has had difficulty keeping food and liquids down since then. The patient has no other medical conditions and takes no medications. Blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 20/min. Urinalysis is positive for glucose and ketones. The patient is given intravenous fluids and an intravenous infusion of recombinant human insulin without any amino acid modification. After his condition is stabilized, the insulin infusion is stopped, and the same insulin formulation is administered subcutaneously. Which of the following drug concentration curves is most likely to be obtained after the subcutaneous insulin injection?



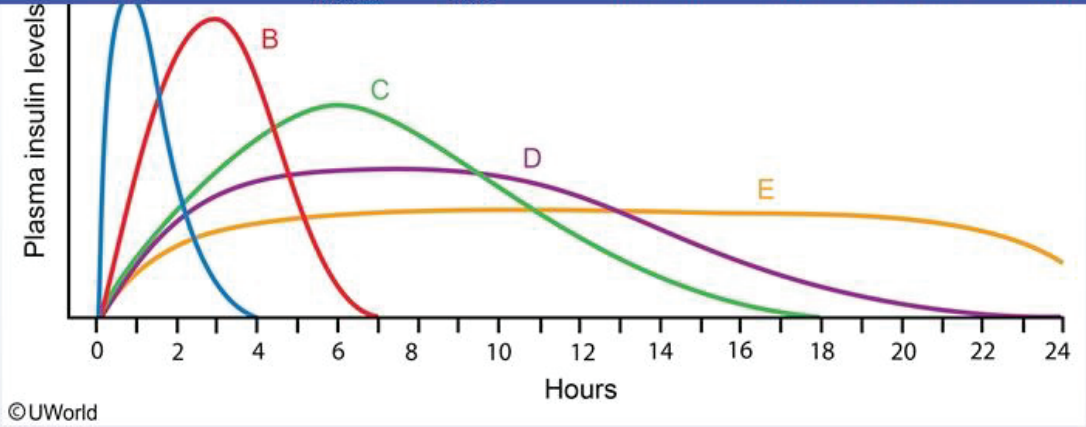
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then. The patient has no other medical conditions and takes no medications. Blood pressure is 90/60 mm Hg, pulse is 120/min, and respirations are 20/min. Urinalysis is positive for glucose and ketones. The patient is given intravenous fluids and an intravenous infusion of recombinant human insulin without any amino acid modification. After his condition is stabilized, the insulin infusion is stopped, and the same insulin formulation is administered subcutaneously. Which of the following drug concentration curves is most likely to be obtained after the subcutaneous insulin injection?

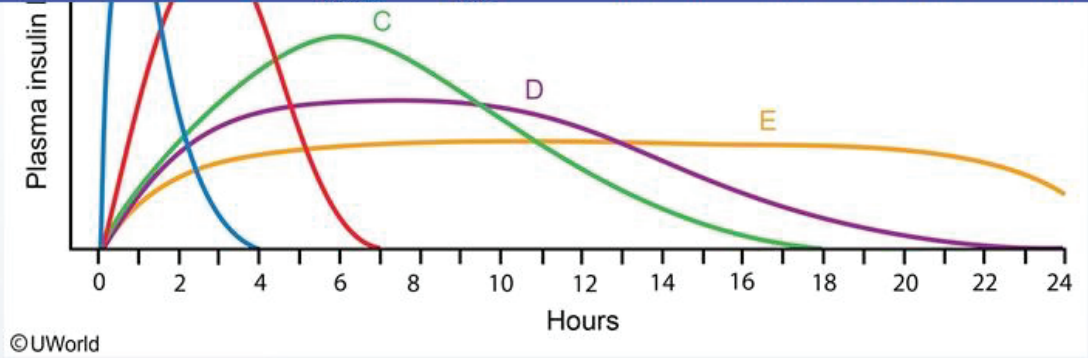


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- A.A
- B.B
- C.C
- D.D
- E.E

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- A. A (9%)
- ✓ B. B (50%)
- C. C (24%)
- D. D (8%)
- E. E (8%)

Correct

50%

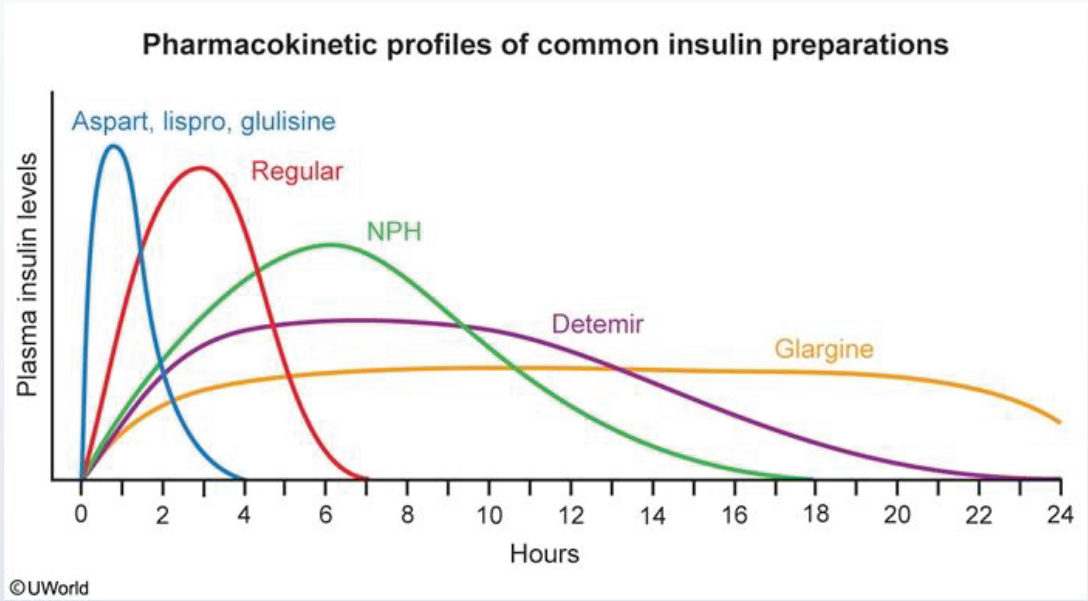
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Explanation



This patient's vomiting, volume depletion, glucosuria, and ketonuria are consistent with **diabetic ketoacidosis** (DKA). DKA is treated with an intravenous infusion of **regular insulin** that begins to lower

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This patient's vomiting, volume depletion, glucosuria, and ketonuria are consistent with **diabetic ketoacidosis** (DKA). DKA is treated with an intravenous infusion of **regular insulin** that begins to lower serum glucose and ketone levels within minutes of administration. Regular insulin has a half-life of 5 minutes when administered **intravenously**, allowing rapid adjustment of the infusion rate based on glucose levels.

Regular insulin can also be used subcutaneously in the subacute and chronic management of diabetes, usually in combination with an intermediate-acting or a long-acting insulin analog to provide bolus and basal coverage. When given **subcutaneously**, regular insulin can polymerize into hexamers, which slightly delays systemic absorption; it starts working within 30 minutes, **peaks in 2-4 hours**, and lasts 5-8 hours.

Regular insulin and neutral protamine Hagedorn (NPH) are the only human recombinant insulins without any modifications in the amino acid sequence. All other insulin preparations (eg, detemir, glargine, lispro, aspart, glulisine) have structural modifications (eg, amino acid modifications) and are considered **insulin analogs**.

(Choice A) Insulin lispro, aspart, and glulisine are rapid-acting insulin analogs. Due to various amino acid modifications, they do not form hexamers like regular insulin, and are absorbed more quickly after

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analogs.

(Choice A) Insulin lispro, aspart, and glulisine are rapid-acting insulin analogs. Due to various amino acid modifications, they do not form hexamers like regular insulin, and are absorbed more quickly after subcutaneous injection. They have an onset of action of about 15 minutes and peak in 45-75 minutes.

(Choice C) NPH insulin is an intermediate-acting insulin composed of a crystalline suspension of insulin with protamine and zinc. This delays absorption of insulin from the subcutaneous injection site. NPH usually starts working within 2 hours, peaks in 4-12 hours, and lasts about 18 hours.

(Choice D) Detemir is a long-acting insulin analog with a fatty acid bound to one of the lysine amino acids on the insulin molecule. This fatty acid side chain allows detemir to bind to albumin and slowly dissociate, resulting in prolonged action. It usually starts working within 2 hours, peaks between 3-9 hours, and lasts up to 24 hours.

(Choice E) Glargine is an insulin analog with a long duration of action. Glargine has a pH of 4 and forms a microprecipitate in the subcutaneous tissue after injection, resulting in a very slow release of insulin. Glargine lasts about 24 hours and does not have a pronounced peak. Longer-acting basal insulin analogs (eg, insulin degludec and concentrated glargine) with duration of action >24 hours are also available.

Educational objective:

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usually starts working within 2 hours, peaks in 4-12 hours, and lasts about 18 hours.

(Choice D) Detemir is a long-acting insulin analog with a fatty acid bound to one of the lysine amino acids on the insulin molecule. This fatty acid side chain allows detemir to bind to albumin and slowly dissociate, resulting in prolonged action. It usually starts working within 2 hours, peaks between 3-9 hours, and lasts up to 24 hours.

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Educational objective:

Diabetic ketoacidosis is initially treated with an intravenous infusion of regular insulin, which allows for rapid adjustments in dose based on blood glucose levels. When given subcutaneously, regular insulin starts working within 30 minutes, peaks in 2-4 hours, and lasts 5-8 hours.

References

- New insulin preparations: a primer for the clinician.

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www.ncbi.nlm.nih.gov/pubmed/27176680

In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

A. Alpha-2 adrenergic receptors

B. Beta-2 adrenergic receptors

C. Glucagon-like peptide-1 receptors

D. Histamine H2 receptors

E. Muscarinic M3 receptors

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In a series of animal experiments, the insulin concentration in the pancreatic veins is measured after the administration of various agents. Epinephrine administration is found to cause a decrease in insulin levels. However, after pretreatment with Drug A, epinephrine injection causes a paradoxical increase in insulin concentration. Which of the following receptors does Drug A most likely block?

- A. Alpha-2 adrenergic receptors (41%)
- B. Beta-2 adrenergic receptors (37%)
- C. Glucagon-like peptide-1 receptors (18%)
- D. Histamine H2 receptors (0%)
- E. Muscarinic M3 receptors (1%)

Correct

41%
Answered correctly

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Explanation

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G protein-coupled receptors on pancreatic beta cells		
Receptor	**G alpha subunit**	**Insulin secretion**
Muscarinic M3	G_q	↑
Glucagon	G_s/ G_q	
• Beta-2 adrenergic • Glucagon-like peptide-1	G_s	
• Alpha-2 adrenergic • Somatostatin 2	G_i	↓

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Pancreatic beta cell insulin secretion is influenced by serum glucose levels and other factors such as autonomic nervous system activity. Parasympathetic stimulation of muscarinic M3 receptors promotes insulin secretion and is induced by the smell and/or sight of food. In contrast, sympathetic stimulation is more complex, since both alpha-2 and beta-2 adrenergic receptors are present on pancreatic beta cells and exert opposite effects. Stimulation of beta-2 receptors promotes insulin secretion while stimulation of alpha-2 receptors inhibits insulin release. However, the alpha-2-mediated inhibitory effect is predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion. Likewise, epinephrine

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(Choice B) Stimulation of beta-2 adrenergic receptors results in increased insulin secretion; beta-2 receptor blockade would inhibit insulin release.

(Choice C) Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the intestinal L cells in response to food and acts on receptors found on pancreatic beta cells to potentiate glucose-induced insulin release. Blocking GLP-1 receptors reduces insulin release. GLP-1 receptor agonists (eg, exenatide, liraglutide) are commonly used to treat type 2 diabetes mellitus.

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(Choice C) Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the intestinal L cells in response to food and acts on receptors found on pancreatic beta cells to potentiate glucose-induced insulin release. Blocking GLP-1 receptors reduces insulin release. GLP-1 receptor agonists (eg, exenatide, liraglutide) are commonly used to treat type 2 diabetes mellitus.

(Choice D) Histamine H2 receptor stimulation increases insulin secretion. Blocking these receptors would cause a decrease in insulin release.

(Choice E) Parasympathetic stimulation increases insulin secretion via M3 muscarinic receptors. Blocking these receptors would inhibit the release of insulin.

Educational objective:

Alpha-2 adrenergic receptors inhibit insulin secretion, and beta-2 adrenergic receptors stimulate insulin secretion. The alpha-2-mediated inhibitory effect is generally predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion.

References

- G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes.

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A 34-year-old man is admitted to the hospital after sustaining a head injury and fractures of both femurs in a motor vehicle collision. CT scan of the head reveals a left-sided extradural hematoma. He has no history of chronic illness and takes no medications. The patient receives intravenous fluid boluses and blood transfusions and is taken to the operating room for fracture repair and removal of the hematoma. On the first postoperative day, laboratory results show high plasma glucose and lactate levels. Which of the following is the primary contributor to this patient's elevated blood glucose levels?

A. Administration of intravenous fluid boluses
B. Decreased hepatic glycerol supply
C. Increased anaerobic glycolysis
D. Increased hepatic glucose production
E. Increased renal gluconeogenesis

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A 34-year-old man is admitted to the hospital after sustaining a head injury and fractures of both femurs in a motor vehicle collision. CT scan of the head reveals a left-sided extradural hematoma. He has no history of chronic illness and takes no medications. The patient receives intravenous fluid boluses and blood transfusions and is taken to the operating room for fracture repair and removal of the hematoma. On the first postoperative day, laboratory results show high plasma glucose and lactate levels. Which of the following is the primary contributor to this patient's elevated blood glucose levels?

A. Administration of intravenous fluid boluses (9%)
B. Decreased hepatic glycerol supply (2%)
C. Increased anaerobic glycolysis (19%)
✓ D. Increased hepatic glucose production (64%)
E. Increased renal gluconeogenesis (4%)

Correct

64%
Answered correctly

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Explanation

Stress hyperglycemia	
Presentation	• Transient hyperglycemia without known diabetes
Risk factors	• Hemorrhage, major trauma • Hypoxia • Sepsis
Pathogenesis	• Secretion of cortisol, catecholamines, glucagon & proinflammatory cytokines • Increased hepatic glycogenolysis & gluconeogenesis

Stress hyperglycemia is a transiently elevated blood glucose level in the context of severe illness in patients without preexisting diabetes mellitus. It is common in the intensive care unit and is typically seen in those with sepsis and other severe infections, burns, trauma, or major hemorrhage.

Severe metabolic stress is associated with increased production of **cortisol**, **catecholamines** (primarily epinephrine and norepinephrine), glucagon, and proinflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha). Cortisol, catecholamines, and glucagon act on the liver to **increase glycogenolysis and**

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Severe metabolic stress is associated with increased production of **cortisol**, **catecholamines** (primarily epinephrine and norepinephrine), glucagon, and proinflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha). Cortisol, catecholamines, and glucagon act on the liver to **increase glycogenolysis and gluconeogenesis**, stimulating release of glucose from the liver into the blood.

In addition, the release of proinflammatory cytokines is associated with increased expression of glucose transporter (GLUT) 1 in the CNS and macrophages, along with decreased expression of GLUT4 (which mediates insulin-induced glucose uptake in peripheral tissues). This facilitates **increased glucose uptake by the brain** and **immune cells** responsible for fighting infection.

(Choice A) During trauma resuscitation, most patients are given isotonic fluids (eg, normal saline, Ringer lactate), which are unlikely to cause hyperglycemia. Even if mild fluid-induced hyperglycemia occurs, blood glucose levels typically normalize quickly after fluid boluses.

(Choice B) Norepinephrine stimulates peripheral lipolysis, releasing glycerol, which can be taken up by the liver for use in gluconeogenesis. Therefore, stress increases, not decreases, the hepatic glycerol supply.

(Choice C) Severe illness is often associated with increased anaerobic glycolysis due to systemic or local tissue hypoxia (blood loss in this patient). Increased conversion of glucose to lactate in ischemic

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glucose levels typically normalize quickly after fluid boluses.

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(Choice C) Severe illness is often associated with increased anaerobic glycolysis due to systemic or local tissue hypoxia (blood loss in this patient). Increased conversion of glucose to lactate in ischemic tissues *raises plasma lactate levels*. Glucose levels are often concurrently elevated due to stress hyperglycemia, but anaerobic glycolysis itself depletes glucose.

(Choice E) The renal cortex can convert lactate to glucose via gluconeogenesis. However, it makes a significantly smaller contribution to circulating glucose levels than hepatic gluconeogenesis.

Educational objective:
Stress hyperglycemia is transiently elevated blood glucose levels in the context of severe illness (eg, sepsis, burns, major hemorrhage) in patients without preexisting diabetes mellitus. Cortisol and catecholamines released in response to severe metabolic stress act on the liver to increase glycogenolysis and gluconeogenesis.

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A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care physician noted an elevated fasting serum glucose level. The endocrinologist discusses the different treatment options available, including oral and injectable medications. He recommends treatment with a medication that alters glucose metabolism within the liver by increasing the concentration of fructose 2,6-bisphosphate within hepatocytes. Which of the following conversions will be inhibited by high intracellular concentrations of this metabolite?

A. Acetyl CoA → fatty acids

B. Alanine → glucose

C. Fructose-6-phosphate → fructose-1,6-bisphosphate

D. Glucose → glycogen

E. NAD^+ → NADH

Submit

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A. Acetyl CoA → fatty acids (3%)

✓ B. Alanine → glucose (37%)

C. ~~Fructose-6-phosphate → fructose-1,6-bisphosphate~~ (43%)

D. ~~Glucose → glycogen~~ (10%)

E. ~~$NAD^+ \rightarrow NADH$~~ (5%)

Correct

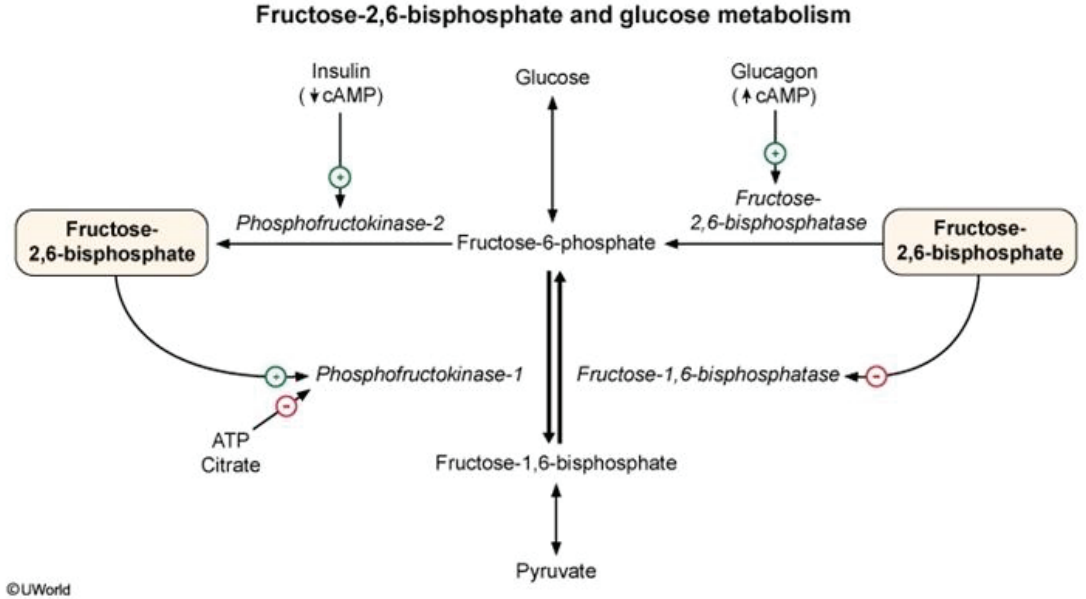
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Fructose 2,6-bisphosphate helps control the balance between **gluconeogenesis** and **glycolysis** through inverse regulation of phosphofructokinase-1 (PFK-1) and fructose 1,6-bisphosphatase. Fructose 2,6-bisphosphate activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose 6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to fructose-6-phosphate) occurs in gluconeogenesis and is catalyzed by the enzyme fructose-1,6-bisphosphatase (inhibited by fructose 2,6-bisphosphate).

The interconversion of fructose-6-phosphate and fructose 2,6-bisphosphate is achieved by a bifunctional enzyme complex composed of PFK-2 (increases fructose 2,6-bisphosphate levels) and fructose 2,6-bisphosphophatase (decreases fructose 2,6-bisphosphate levels). **Insulin** causes activation of PFK-2, leading to **increased fructose 2,6-bisphosphate levels** and **augmented glycolysis**. High concentrations of fructose 2,6-bisphosphate also **inhibit gluconeogenesis**, leading to **decreased conversion of alanine** and other gluconeogenic substrates to glucose.

(Choice A) Fatty acid synthesis is upregulated by insulin and high citrate levels (which increase when acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the

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acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the enzyme PFK-1. This enzyme is allosterically activated by high levels of fructose-2,6-bisphosphate, and so conversion would be increased.

(Choice D) Glycogen formation is stimulated by increased levels of insulin and glucose-6-phosphate. Because elevated insulin levels also increase fructose 2,6-bisphosphate formation, the rise of fructose 2,6-bisphosphate levels in hepatocytes is typically concurrent with increased glycogen synthesis.

(Choice E) The rise in fructose-2,6-bisphosphate accelerates glycolysis, leading to increased conversion of NAD^+ to NADH.

Educational objective:
Fructose 2,6-bisphosphate (F2,6BP) activates phosphofructokinase-1 (increasing glycolysis) and inhibits fructose 1,6-bisphosphatase (decreasing gluconeogenesis). F2,6BP concentration is regulated by a bifunctional enzyme complex: phosphofructokinase-2 increases F2,6BP levels in response to insulin, and fructose 2,6-bisphosphatase decreases F2,6BP levels in response to glucagon.

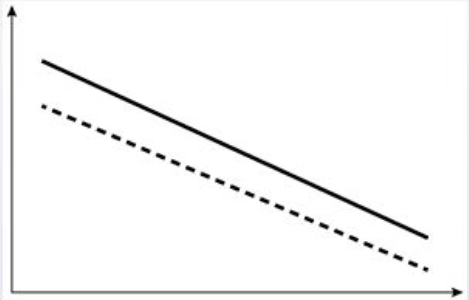
References

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A 60-year-old man comes to the office due to 2 months of low back pain unresponsive to over-the-counter analgesics. The pain is worse at night and interferes with sleep. On examination, the lumbar vertebrae are tender to palpation, and the prostate is indurated and firm. After a thorough evaluation, leuprolide therapy is started. Which of the following changes in testosterone (solid line) and dihydrotestosterone (dashed line) levels are most likely to occur in this patient after initiation of therapy?

A.



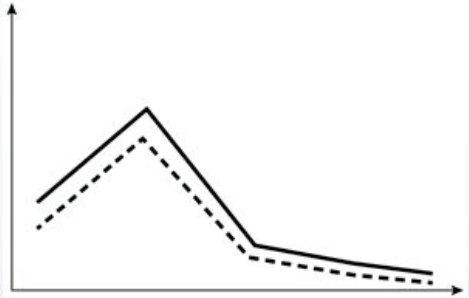
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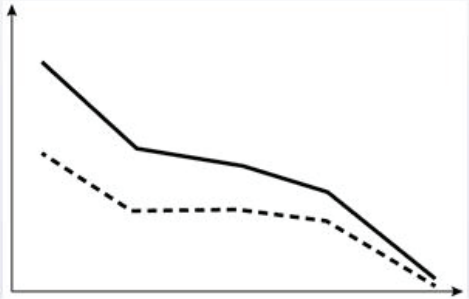
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B.



C.



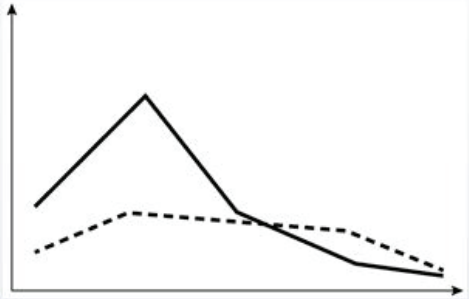
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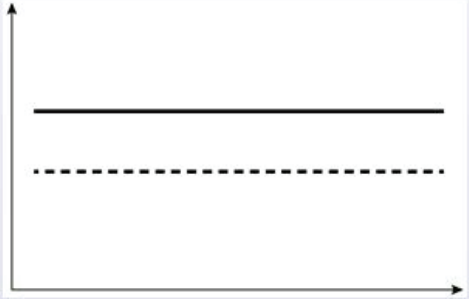
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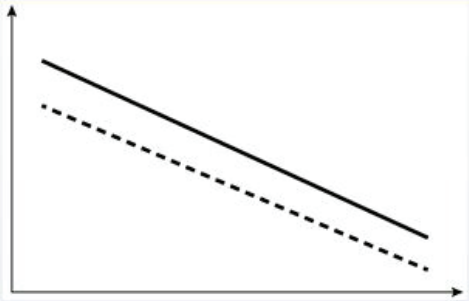


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levels are most likely to occur in this patient after initiation of therapy?

A. (13%)



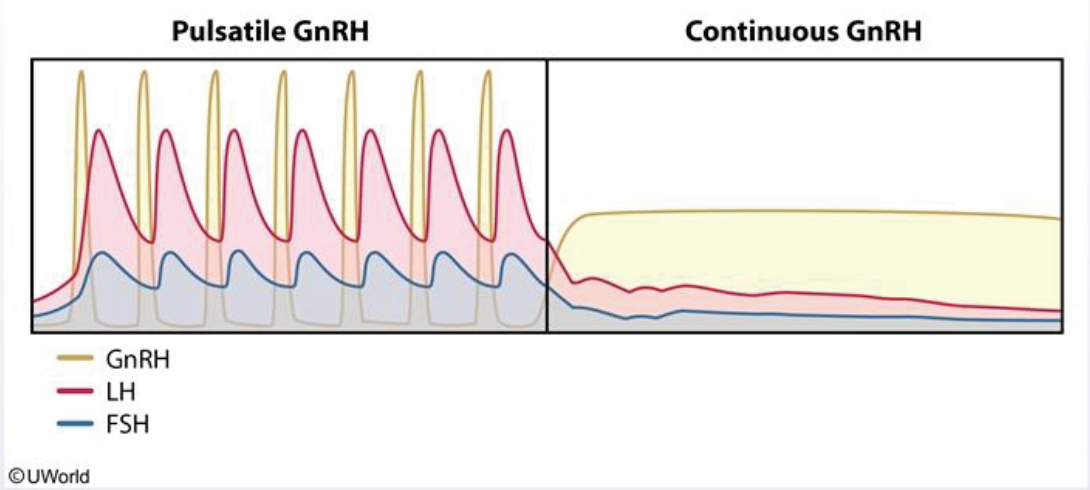
B. (59%)



C. (8%)



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This patient's nocturnal back pain, spinal tenderness, and indurated prostate suggest **prostate adenocarcinoma** with bony metastases. Prostate cancer is an **androgen-dependent** tumor. Because most androgens (eg, testosterone) in men are made in the Leydig cells of the testes, initial treatment focuses on a systemic reduction in androgen production via surgical or medical **orchiectomy**.

Androgen production is primarily regulated by the hypothalamic-pituitary-testicular axis. Neurons in the hypothalamus release **GnRH** into the hypothalamic-pituitary portal system in a **pulsatile pattern** every

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This patient's nocturnal back pain, spinal tenderness, and indurated prostate suggest **prostate adenocarcinoma** with bony metastases. Prostate cancer is an **androgen-dependent** tumor. Because most androgens (eg, testosterone) in men are made in the Leydig cells of the testes, initial treatment focuses on a systemic reduction in androgen production via surgical or medical **orchiectomy**.

Androgen production is primarily regulated by the hypothalamic-pituitary-testicular axis. Neurons in the hypothalamus release **GnRH** into the hypothalamic-pituitary portal system in a **pulsatile pattern** every 90-120 minutes. This stimulates pituitary gonadotrophs to release luteinizing hormone (**LH**) into the circulation, which then binds to a surface receptor on Leydig cells and stimulates androgen production.

In medical orchiectomy, a **GnRH analogue** (eg, **leuprolide**) is administered to continuously stimulate pituitary gonadotrophs, which leads to down-regulation of the GnRH receptor, lower LH release, and reduced testicular androgen production. However, because GnRH analogues **initially stimulate** pituitary gonadotrophs prior to the down-regulation of the receptor, most patients have a **transient increase in systemic androgens** during the first week of therapy (upward portion of graph). This effect is generally blunted by administering a short course of androgen receptor antagonist medication (eg, bicalutamide) during treatment initiation in order to prevent worsening of the underlying prostate cancer.

(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a

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blunted by administering a short course of androgen receptor antagonist medication (eg, bicalutamide) during treatment initiation in order to prevent worsening of the underlying prostate cancer.

(Choices A and C) GnRH analogues stimulate the GnRH receptor prior to down-regulation, resulting in a transient increase in LH and systemic androgen production prior to down-regulation of the receptor.

(Choice D) The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone (DHT) in peripheral tissues (eg, skin, liver); as testosterone levels fall, DHT production will decrease concurrently. GnRH analogues have no effect on the activity of 5-alpha reductase, therefore, testosterone and DHT levels rise and fall in synchrony following GnRH administration.

(Choice E) Benign prostatic hyperplasia is typically treated with a 5-alpha reductase inhibitor (eg, finasteride), which reduces the conversion of testosterone to DHT. This class of medications reduces DHT levels while testosterone levels remain largely unaffected.

Educational objective:

Leuprolide is a GnRH agonist used to treat prostate cancer. It initially stimulates pituitary LH secretion, which leads to a rise in androgen levels. However, the GnRH receptor is subsequently down-regulated, which dramatically drops LH release and leads to a long-term decrease in androgen production.

References

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An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The mother had gestational diabetes during pregnancy, which was controlled by diet alone. Physical examination of the infant shows clitoromegaly and partial fusion of the labioscrotal folds. Cytogenetic analysis reveals a 46,XX karyotype. Abdominal imaging shows bilateral adrenal hyperplasia. This patient is most likely deficient for an enzyme normally responsible for which of the following reactions?

A. Cholesterol → Pregnenolone

B. Dehydroepiandrosterone → Androstenedione

C. Progesterone → 11-deoxycorticosterone

D. Progesterone → 17-hydroxyprogesterone

E. Testosterone → Dihydrotestosterone

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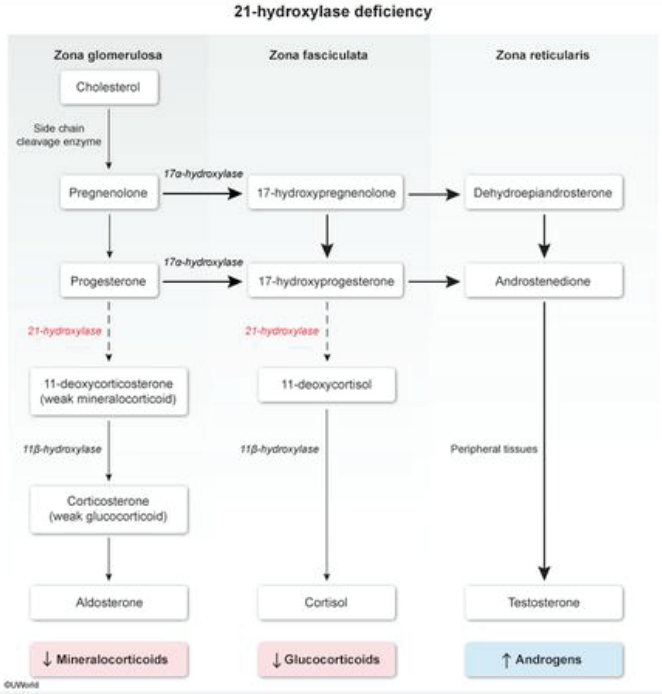
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This patient's abdominal imaging and ambiguous genitalia are consistent with **congenital adrenal hyperplasia** (CAH). The most common cause of CAH is **21-hydroxylase deficiency**, accounting for 90% of all cases. This enzyme catalyzes the conversion of **progesterone to 11-deoxycorticosterone** (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. ACTH levels increase as a result of low cortisol levels, stimulating **increased adrenal androgen** production by diverting the accumulating aldosterone and cortisol precursors toward the androgen biosynthetic pathway. Genetic females (46,XX) affected with classic 21-hydroxylase deficiency are usually identified at birth as increased androgen levels lead to ambiguous genitalia (**virilization**). However, genetic males (46,XY) have normal genitalia and therefore typically present later with symptoms of **salt-wasting** or precocious puberty.

Infants with 21-hydroxylase deficiency are often detected during routine newborn screening, and a high serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to

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(Choice A) Side-c

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21-Hydroxylase deficiency clinical syndromes

	Classic, salt wasting	Classic, non–salt wasting*	Nonclassic, late onset
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		

*Also called simple virilizing form.

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serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to absent placental progesterone synthesis.

(Choice B) Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase, an enzyme that also converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

(Choice D) Synthesis of 17-hydroxyprogesterone from progesterone is catalyzed by 17α-hydroxylase. Deficiency of this enzyme causes mineralocorticoid excess and impaired androgen synthesis. Genetic males have ambiguous genitalia, whereas genetic females appear phenotypically normal.

(Choice E) 5α-reductase deficiency prevents the conversion of testosterone to dihydrotestosterone, the hormone responsible for the development of male external genitalia. Affected genetic males, not females, are born with ambiguous genitalia.

Educational objective:

The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency. Genetically female

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to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

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(Choice E) 5α-reductase deficiency prevents the conversion of testosterone to dihydrotestosterone, the hormone responsible for the development of male external genitalia. Affected genetic males, not females, are born with ambiguous genitalia.

Educational objective:

The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency. Genetically female infants typically have ambiguous genitalia (virilization) at birth, whereas males have phenotypically normal genitalia, with salt-wasting or precocious puberty appearing later. Elevated 17-hydroxyprogesterone is diagnostic.

References

- Congenital adrenal hyperplasia.

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A 55-year-old man comes to the office to establish care after relocating to the area. The patient has a 6-year history of type 2 diabetes mellitus for which he takes metformin monotherapy. He feels well and has no other medical conditions. The patient does not use tobacco or alcohol. He consumes a balanced diet and jogs for 40 minutes every morning. Review of his blood glucose journal over the last few months shows fasting glucose levels of 150-180 mg/dL. Laboratory analysis shows a hemoglobin A1c level of 4%. Further evaluation with hemoglobin electrophoresis shows a hemoglobin A2 level of 7.5% (normal: 1.5%-3.5%). Which of the following is the most likely explanation for this patient's lower-than-expected hemoglobin A1c level?

A. Beta-thalassemia minor
B. Folate deficiency
C. Iron deficiency
D. Low erythropoietin
E. Poor glycemic control
F. Sickle cell trait

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no other medical conditions. The patient does not use tobacco or alcohol. He consumes a balanced diet and jogs for 40 minutes every morning. Review of his blood glucose journal over the last few months shows fasting glucose levels of 150-180 mg/dL. Laboratory analysis shows a hemoglobin A1c level of 4%. Further evaluation with hemoglobin electrophoresis shows a hemoglobin A2 level of 7.5% (normal: 1.5%-3.5%). Which of the following is the most likely explanation for this patient's lower-than-expected hemoglobin A1c level?

- A. Beta-thalassemia minor (76%)
- B. Folate deficiency (1%)
- C. Iron deficiency (2%)
- D. Low erythropoietin (4%)
- E. Poor glycemic control (1%)
- F. Sickle cell trait (12%)

Correct

76%

01 min, 09 secs

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Hemoglobin A1c is produced by irreversible nonenzymatic glycosylation of the N-terminal of the hemoglobin molecule. The degree of glycosylation (ie, hemoglobin A1c level) directly correlates with average blood glucose levels over the life span of circulating erythrocytes, which is normally approximately 3 months. **Higher glucose levels** and **increased exposure time** of red cells to glucose **increase hemoglobin A1c** values. As such, conditions that alter red blood cell survival time also affect hemoglobin A1c levels.

This patient has an elevated hemoglobin A2, which suggests comorbid **beta-thalassemia minor**. Hemoglobin A2 is elevated in beta-thalassemia to compensate for beta-globin–chain underproduction, but results in microcytic red cells that are prone to hemolysis. **Increased erythrocyte turnover** results in a **misleadingly low hemoglobin A1c level**. In such cases, measurement of glycated serum proteins (ie, fructosamine) is sometimes used to estimate glycemic control.

(Choices B and C) Deficiencies of iron, folate, and vitamin B_{12} can reduce production of new red cells, leading to a preponderance of older erythrocytes and falsely elevated hemoglobin A1c. In contrast, treatment of vitamin deficiencies causes young red cells to be rapidly released into circulation, falsely lowering hemoglobin A1c.

(Choice D) Advanced diabetic nephropathy may cause reduced erythropoietin production. The resulting

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Hemoglobin electrophoresis patterns in sickle cell & beta-thalassemia				
Condition	**Hemoglobin A**	**Hemoglobin A2**	**Hemoglobin F**	**Hemoglobin S**
Normal	95%-98%	~2.5%	<1%	Absent
Beta-thalassemia minor	↓	↑	Near normal	Absent
Beta-thalassemia major	Absent	↑↑	↑↑	Absent
Sickle cell trait	↓↓	Near normal	Near normal	↑
Sickle cell disease	Absent	Near normal	↑↑	↑↑

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(Choice D) Advanced diabetic nephropathy may cause reduced erythropoietin production. The resulting decrease in production of new red cells may lead to falsely high hemoglobin A1c (similar to nutrient deficiencies).

(Choice E) Chronically elevated blood glucose (ie, poor glycemic control) is the primary cause of increased hemoglobin A1c in patients with diabetes.

(Choice F) Sickle cell trait is characterized by heterozygous carriage of hemoglobin S. Some patients with sickle cell trait can have slightly reduced hemoglobin A1c level due to increased red cell turnover (homozygous individuals with sickle cell disease have rapid red cell turnover and very low A1c). However, hemoglobin A2 percentage remains near normal in patients with sickle cell mutations.

Educational objective:

Hemoglobin A1c is produced by nonenzymatic glycosylation of the hemoglobin molecule. A hemoglobin A1c assay provides an estimate of chronic glycemic control over the life span of circulating erythrocytes (~3 months). However, rapid erythrocyte turnover (eg, hemolytic anemia) can give a misleadingly low hemoglobin A1c in relation to glycemic status.

References

- Limitations of A1c interpretation.

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A 25-year-old man comes to the office for evaluation of facial acne. He has no significant past medical history and does not use tobacco or alcohol. The patient works as a personal trainer. His family history is significant for diabetes mellitus in his mother and leukemia in his father. His blood pressure is 134/82 mm Hg and pulse is 58/min. On physical examination, there is mild facial acne. The patient's lungs are clear to auscultation. The liver span is 8 cm, and the spleen is not palpable. His testes are soft, and testicular volume is decreased. Laboratory results are as follows:

Hematocrit	60%
White blood cells	7,500/mm^3
Platelets	225,000/mm^3
Erythrocyte sedimentation rate	15 mm/hr
Serum creatinine	1.2 mg/dL
Blood urea nitrogen	18 mg/dL

Which of the following is the most likely explanation for this patient's abnormal laboratory findings?

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Erythrocyte sedimentation rate	15 mm/hr
Serum creatinine	1.2 mg/dL
Blood urea nitrogen	18 mg/dL

Which of the following is the most likely explanation for this patient's abnormal laboratory findings?

A. High oxygen affinity hemoglobin
B. Intensive exercise schedule
C. Myeloproliferative disorder
D. Renal artery stenosis
E. Steroid drug abuse
F. Volume depletion due to excessive sweating

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Platelets	225,000/mm³
Erythrocyte sedimentation rate	15 mm/hr
Serum creatinine	1.2 mg/dL
Blood urea nitrogen	18 mg/dL

Which of the following is the most likely explanation for this patient's abnormal laboratory findings?

A. High oxygen affinity hemoglobin (1%)
B. Intensive exercise schedule (4%)
C. Myeloproliferative disorder (3%)
D. Renal artery stenosis (1%)
✓ E. Steroid drug abuse (86%)
F. Volume depletion due to excessive sweating (3%)

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Explanation

Effects of androgen abuse	
Cardiovascular	• ↑ **Hematocrit** • ↑ LDL, ↓ HDL cholesterol
Dermatologic	• **Acne** • Hirsutism, male-pattern hair loss (♀)
Genitourinary	• Clitoromegaly, oligomenorrhea (♀) • **Testicular atrophy**, ↓ spermatogenesis (♂)
Psychiatric	• Depression, hypomania (♀) • Aggressiveness, mood disorders (♂)
Breast	• Atrophy (♀) • **Gynecomastia** (♂)
Other	• **Deepening of voice** (♀) • Premature epiphyseal closure (adolescents)

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This patient has acne, testicular atrophy, and erythrocytosis, findings concerning for **androgenic steroid abuse**. Abuse of androgens, androgen precursors, and agents that increase endogenous androgen production is most common in young adults who engage in competitive athletic activities or for cosmetic purposes.

Chronic androgen use may increase muscle mass but has multiple associated risks. Testosterone stimulates red blood cell production, which accounts for the higher hematocrit in normal males compared to normal females. This effect is exaggerated in exogenous androgen abuse, which **increases hematocrit** in a dose-dependent manner. Androgens decrease gonadotropin secretion, which results in **testicular atrophy** and decreased sperm production. Other common findings include **virilization** in women (eg, clitoromegaly, hirsutism) and **acne**.

(Choices A and D) Mutations that cause a high oxygen affinity of hemoglobin reduce the ability of hemoglobin to release oxygen in tissues. Low tissue oxygen levels in the kidneys stimulate erythropoietin release. Renal artery stenosis decreases oxygen delivery to the kidney and also stimulates erythropoietin release. These conditions may produce a compensatory erythrocytosis but would not produce the other clinical signs (eg, acne, testicular atrophy) seen in this patient.

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release. These conditions may produce a compensatory erythrocytosis but would not produce the other clinical signs (eg, acne, testicular atrophy) seen in this patient.

(Choice B) Intensive exercise could result in elevated myoglobin secondary to rhabdomyolysis, but the hematocrit level should not be changed by exercise.

(Choice C) Myeloproliferative disorders, such as polycythemia vera (PV), can lead to erythrocytosis. Patients with PV typically have leukocytosis and thrombocytosis as well. This patient's additional physical findings make steroid abuse more likely.

(Choice F) Heavy sweating may cause a transient increase in hematocrit due to loss of plasma volume but would likely cause other signs of dehydration (eg, tachycardia). This patient's creatinine at the upper limit of normal is typical for patients with increased total muscle mass; hypovolemia also will usually cause a more pronounced rise in blood urea nitrogen.

Educational objective:
Androgenic steroid abuse may lead to erythrocytosis, testicular atrophy, acne, and virilization in women (eg, clitoromegaly, hirsutism).

References

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www.ncbi.nlm.nih.gov/pubmed/18160461

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A 45-year-old man comes to the office due to a 6-month history of headache, sweating, and pain in his lower back, knees, and small joints of his hands. The pain increases with physical activity. He is unable to remove his wedding ring due to swollen fingers. The patient has also experienced excessive urination and loss of libido. Examination shows a prominent jaw and enlarged supraorbital ridges. The patient's hands are notably broad with thickened fingers. Multiple skin tags are noted on the nape of the neck. Laboratory evaluation reveals low serum testosterone levels. Which of the following is the most likely underlying cause of this patient's joint symptoms?

A. Accumulation of iron
B. Deposition of crystals
C. Formation of noncaseating granulomas
D. Hypertrophy of the articular cartilage
E. Infiltration of macrophages

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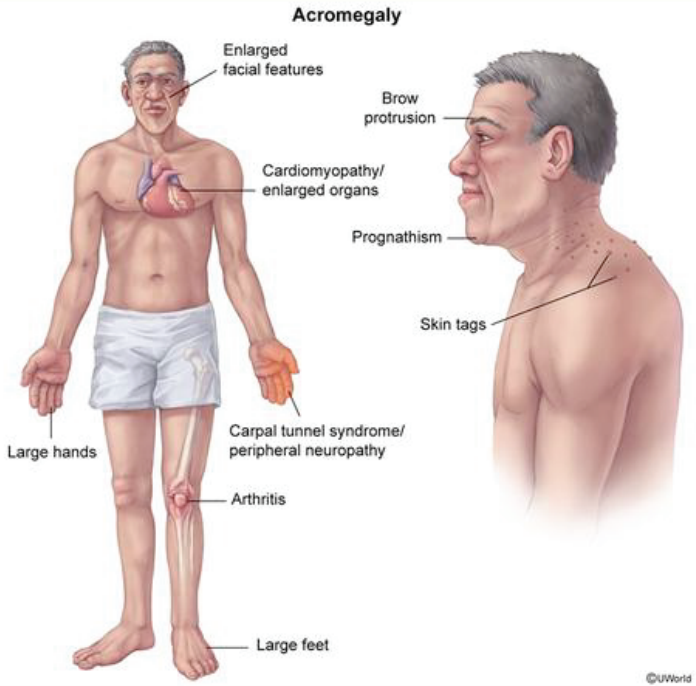
A. Accumulation of iron (10%)
B. Deposition of crystals (5%)
C. Formation of noncaseating granulomas (3%)
D. Hypertrophy of the articular cartilage (75%)
E. Infiltration of macrophages (4%)

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This patient has common features of **acromegaly**, including coarsening of facial features (eg, brow protrusion, prognathism), broadening of the hands, and skin involvement (eg, skin tags, hyperhidrosis). Acromegaly is caused by excessive production of **growth hormone** (GH) and is most often due to a **pituitary somatotroph adenoma**. Excess GH both directly and indirectly (via release of insulin-like growth factor-1 from the liver) leads to overgrowth of many tissues, including bone, cartilage, and visceral organs.

Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive GH causes **hyperplasia of articular chondrocytes** and **synovial hypertrophy**, which may appear on x-ray as widening of the joint space. As acromegalic arthropathy continues, there is degeneration of articular cartilage and periarticular bone resembling osteoarthritis.

Complications of the pituitary mass itself include headache, visual field defects (compression of optic chiasm), and abnormalities of other pituitary hormones. **Hypogonadism** can occur secondary to hyperprolactinemia (from disrupted negative regulation of prolactin secretion) or directly due to compression of pituitary gonadotrophs.

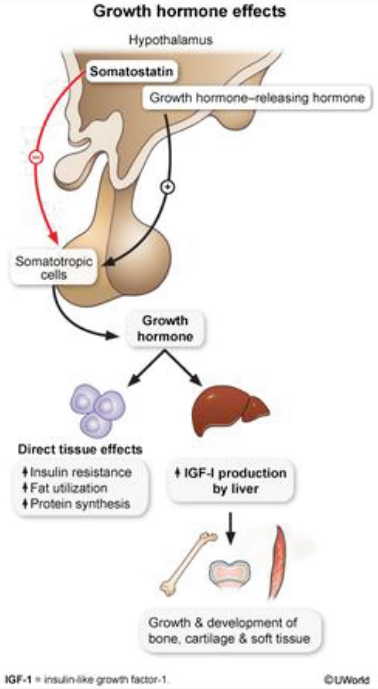
(Choice A) Hereditary hemochromatosis (HH) can cause arthritis due to accumulation of iron in the articular cartilage and synovium. Although HH can also cause central hypogonadism, this patient's skeletal and facial features are more consistent with acromegaly

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(Choice A) Hereditary hemochromatosis (HH) can cause arthritis due to accumulation of iron in the articular cartilage and synovium. Although HH can also cause central hypogonadism, this patient's skeletal and facial features are more consistent with acromegaly.

(Choice B) Crystal deposition arthritis typically presents initially with acute inflammatory monarthritis at the first metatarsophalangeal joints and knees (gout), or knees, wrists, shoulders, and elbows (pseudogout [ie, calcium pyrophosphate deposition arthritis]). These disorders would not cause facial changes or hypogonadism.

(Choice C) Sarcoidosis is characterized by the formation of noncaseating granulomas in various tissues. Sarcoid arthropathy often occurs acutely in association with erythema nodosum and hilar adenopathy (Lofgren syndrome); chronic arthritis is less common and usually occurs in patients with significant pulmonary disease.

(Choice E) Rheumatoid arthritis (RA) involves a complex inflammatory response, culminating in an influx of monocytes that differentiate into inflammatory macrophages in the synovium. RA commonly presents with chronic swelling of the metacarpophalangeal joints but does not cause enlargement of the supraorbital ridges or jaw.

Educational objective:

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www.ncbi.nlm.nih.gov/pubmed/18160461

hypogonadism.

(Choice C) Sarcoidosis is characterized by the formation of noncaseating granulomas in various tissues. Sarcoid arthropathy often occurs acutely in association with erythema nodosum and hilar adenopathy (Lofgren syndrome); chronic arthritis is less common and usually occurs in patients with significant pulmonary disease.

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Educational objective:
Acromegaly can affect the joints in both the axial and the appendicular skeleton. Excessive growth hormone and insulin-like growth factor-1 cause hyperplasia of articular chondrocytes and synovial hypertrophy, leading to later degeneration of articular cartilage and periarticular bone.

Pathology	Endocrine, Diabetes & Metabolism	Acromegaly
Subject	System	Topic

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www.ncbi.nlm.nih.gov/pubmed/18160461

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A 35-year-old woman is evaluated for a 3-month history of appetite loss, fatigue, weight loss, and abdominal pain. She has no chronic medical conditions and takes no medications. While undergoing upper gastrointestinal endoscopy, the patient develops cardiovascular collapse and dies, despite aggressive resuscitative measures. On autopsy, increased pigmentation is noted around the nipple areola and anal and vaginal mucous membranes. Which of the following additional findings are most likely to be seen on autopsy?

A. Atrophy of both adrenal glands
B. Bilateral adrenal hemorrhage
C. Ischemic anterior pituitary necrosis
D. Large pituitary tumor with hemorrhage
E. Unilateral adrenal mass with contralateral adrenal atrophy

Submit

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www.ncbi.nlm.nih.gov/pubmed/18160461

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

A 35-year-old woman is evaluated for a 3-month history of appetite loss, fatigue, weight loss, and abdominal pain. She has no chronic medical conditions and takes no medications. While undergoing upper gastrointestinal endoscopy, the patient develops cardiovascular collapse and dies, despite aggressive resuscitative measures. On autopsy, increased pigmentation is noted around the nipple areola and anal and vaginal mucous membranes. Which of the following additional findings are most likely to be seen on autopsy?

- ✓ A. Atrophy of both adrenal glands (52%)
- B. Bilateral adrenal hemorrhage (18%)
- C. Ischemic anterior pituitary necrosis (4%)
- D. Large pituitary tumor with hemorrhage (12%)
- E. Unilateral adrenal mass with contralateral adrenal atrophy (12%)

Correct

52% Answered correctly

01 min, 19 secs Time Spent

11/03/2020 Last Updated

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www.ncbi.nlm.nih.gov/pubmed/18160461

Primary adrenal insufficiency	
Etiology	• **Autoimmune adrenalitis** (most common) • Infection (eg, tuberculosis) • Hemorrhagic infarction
Clinical features	• Fatigue, weakness, anorexia/weight loss • Nausea/vomiting/abdominal pain • Postural hypotension • Hyperpigmentation • **Acute adrenal crisis:** confusion, shock
Laboratory findings	• Hyponatremia, hyperkalemia • Low morning cortisol, high ACTH • Eosinophilia

This patient with a three month history of weight loss, abdominal pain, and fatigue developed cardiovascular collapse during a medical procedure (endoscopy), which suggests **chronic adrenal insufficiency** complicated by **acute adrenal crisis**. Severe physiologic stress (eg, infection, medical

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	• Eosinophilia

This patient with a three month history of weight loss, abdominal pain, and fatigue developed cardiovascular collapse during a medical procedure (endoscopy), which suggests **chronic adrenal insufficiency** complicated by **acute adrenal crisis**. Severe physiologic stress (eg, infection, medical procedures) normally induces increased glucocorticoid production; however, patients with adrenal insufficiency are unable to increase production. Adrenal crisis (eg, hypotension, shock) is rapidly fatal if unrecognized.

Adrenal insufficiency can be caused by dysfunction of either the adrenal glands (primary) or pituitary (secondary). This patient's concomitant **skin hyperpigmentation** is highly suggestive of chronic **primary adrenal insufficiency** (PAI), as the resulting cortisol deficiency leads to increased ACTH secretion. ACTH is derived from proopiomelanocortin (POMC), the same prohormone from which melanocyte-stimulating hormone (MSH) is derived. Increased ACTH also leads to increased MSH secretion, which results in hyperpigmentation.

Autoimmune adrenalitis is the most common cause (>90%) of chronic PAI and occurs due to autoantibody formation, resulting in **atrophy of the bilateral adrenal glands**. It can occur as an isolated disorder or in association with other autoimmune syndromes (eg, hypothyroidism, vitiligo).

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www.ncbi.nlm.nih.gov/pubmed/18160461

Autoimmune adrenalitis is the most common cause (>90%) of chronic PAI and occurs due to autoantibody formation, resulting in **atrophy of the bilateral adrenal glands**. It can occur as an isolated disorder or in association with other autoimmune syndromes (eg, hypothyroidism, vitiligo).

(Choice B) Bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome [WFS]) can cause PAI and adrenal crisis but is typically seen *acutely* in the setting of bacterial sepsis (eg, *Neisseria meningitidis*). However, hyperpigmentation occurs in *chronic* adrenal insufficiency and therefore would not be expected with WFS.

(Choices C and D) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary gland during childbirth. Acute pituitary hemorrhage (pituitary apoplexy) typically occurs in patients with pituitary adenomas. These conditions can cause central (secondary) adrenal insufficiency; however, hyperpigmentation is not seen because ACTH levels are low, and POMC levels are not increased.

(Choice E) A cortisol-producing adrenal tumor can cause contralateral adrenal atrophy due to suppression of ACTH secretion; however, it would not be associated with hyperpigmentation and would manifest as hypercortisolism rather than adrenal insufficiency.

Educational objective:

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www.ncbi.nlm.nih.gov/pubmed/18160461

with WFS.

(Choices C and D) Ischemic necrosis of the pituitary (Sheehan syndrome) most commonly occurs due to hypoperfusion of the enlarged pituitary gland during childbirth. Acute pituitary hemorrhage (pituitary apoplexy) typically occurs in patients with pituitary adenomas. These conditions can cause central (secondary) adrenal insufficiency; however, hyperpigmentation is not seen because ACTH levels are low, and POMC levels are not increased.

(Choice E) A cortisol-producing adrenal tumor can cause contralateral adrenal atrophy due to suppression of ACTH secretion; however, it would not be associated with hyperpigmentation and would manifest as hypercortisolism rather than adrenal insufficiency.

Educational objective:
Primary adrenal insufficiency (PAI) is characterized by weight loss, abdominal pain, fatigue, and hyperpigmentation. Physiologic stress in patients with PAI can trigger acute adrenal crisis (eg, fever, shock, mental status changes). Autoimmune adrenalitis is the most common cause of PAI and leads to bilateral adrenal atrophy.

References

- Diagnosis and classification of Addison's disease (autoimmune adrenalitis).

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www.ncbi.nlm.nih.gov/pubmed/18160461

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

A 51-year-old woman comes to the office due to progressively worsening fatigue, weight gain, and constipation for the past 6 months. The patient has had difficulty performing daily activities due to fatigue. She has no significant medical history and takes no medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 110/80 mm Hg and pulse is 55/min. Physical examination shows mild, diffuse enlargement of the thyroid gland. Cardiopulmonary and abdominal examinations are normal. Biopsy of this patient's thyroid is most likely to show which of the following findings?

A. Branching papillae with cells containing empty-appearing nuclei
B. Dense fibrous tissue extending beyond the thyroid capsule
C. Follicular hyperplasia with tall cells projecting into the follicular lumen
D. Intense lymphoplasmacytic infiltrate with active germinal centers
E. Widespread inflammatory infiltrates, giant cells, and disrupted follicles

Submit

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27

A 51-year-old woman comes to the office due to progressively worsening fatigue, weight gain, and constipation for the past 6 months. The patient has had difficulty performing daily activities due to fatigue. She has no significant medical history and takes no medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 110/80 mm Hg and pulse is 55/min. Physical examination shows mild, diffuse enlargement of the thyroid gland. Cardiopulmonary and abdominal examinations are normal. Biopsy of this patient's thyroid is most likely to show which of the following findings?

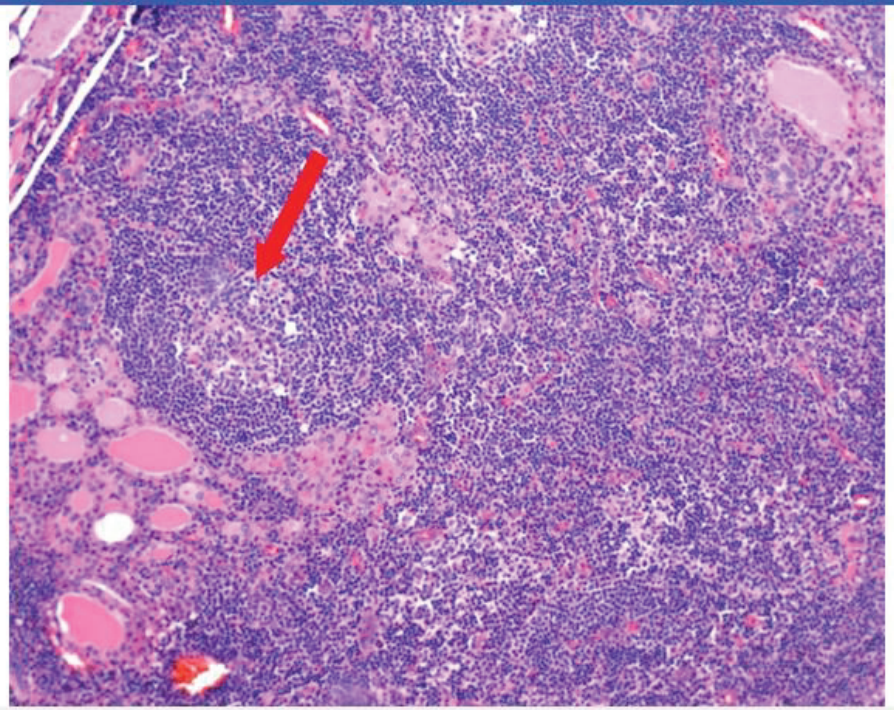
A. Branching papillae with cells containing empty-appearing nuclei (6%)
B. Dense fibrous tissue extending beyond the thyroid capsule (5%)
C. Follicular hyperplasia with tall cells projecting into the follicular lumen (10%)
D. Intense lymphoplasmacytic infiltrate with active germinal centers (52%)
E. Widespread inflammatory infiltrates, giant cells, and disrupted follicles (24%)

52% 01 min, 08 secs 09/13/2020

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This patient has progressive symptoms of hypothyroidism (eg, fatigue, weight gain, constipation) and a diffuse goiter, consistent with **chronic lymphocytic (Hashimoto) thyroiditis**. This disease occurs predominately in women, with a peak incidence at age 45-65, and is the most common cause of hypothyroidism in iodine-sufficient regions such as the United States.

As with all forms of primary hypothyroidism, laboratory studies show low serum thyroxine (T4) levels and an elevated TSH. Elevated antithyroid peroxidase antibody levels can confirm the diagnosis. If the diagnosis is uncertain (eg, thyroid nodularity), a biopsy can be performed to rule out malignancy. Characteristic findings of Hashimoto thyroiditis include an intense **mononuclear infiltrate** consisting of **lymphocytes** and plasma cells, often with **germinal centers** (arrow in image above). Residual follicles are often surrounded by **Hürthle cells** (large oxyphilic cells filled with granular cytoplasm) that represent follicular epithelial cells that have undergone metaplastic change in response to inflammation.

(Choice A) Histopathology in papillary thyroid cancer shows branching papillary structures with concentric calcifications (psammoma bodies) and ground-glass or empty-appearing nuclei ("Orphan Annie eye" nuclei). However, papillary thyroid cancer typically presents as an enlarging nodule in a clinically euthyroid patient.

(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid gland extending into the

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(Choice B) Riedel thyroiditis is characterized by extensive fibrosis of the thyroid gland extending into the surrounding structures. The fibrotic thyroid gland in Riedel thyroiditis is typically hard and fixed to surrounding structures, often resembling a malignancy.

(Choice C) Graves disease presents with a diffusely enlarged thyroid gland associated with hyperthyroidism, exophthalmos, and pretibial myxedema. The thyroid follicular epithelium is tall and crowded with hyperactive reabsorption, causing scalloping around the edges of the colloid. Follicular hyperplasia with elongated epithelial cells is also seen in the tall-cell variant of papillary thyroid cancer, typically presenting in older adults as an enlarging thyroid mass.

(Choice E) Subacute granulomatous (de Quervain) thyroiditis is characterized by disruption of follicles and a mixed cellular infiltrate with occasional multinuclear giant cells. Patients typically present after a viral upper respiratory infection with fever and a painful, tender thyroid gland.

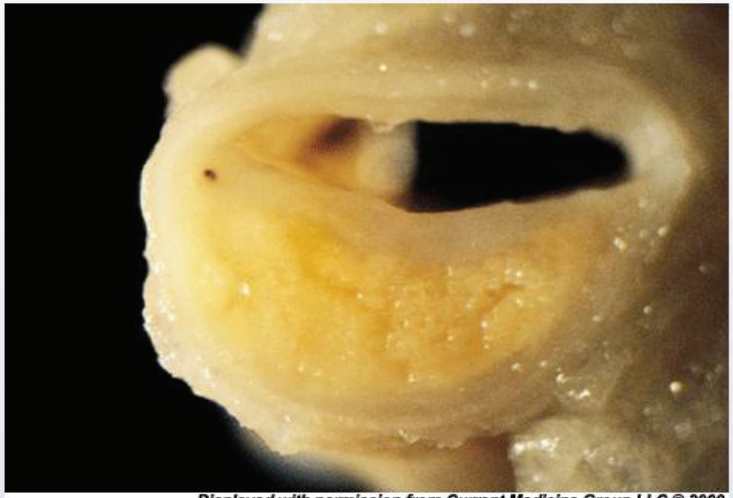
Educational objective:

Chronic lymphocytic (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Histopathology characteristically shows an intense lymphocytic infiltrate, often with germinal centers. Residual follicles may be surrounded by Hürthle cells (large oxyphilic cells filled with granular cytoplasm).

References

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A cross-section of the right coronary artery of a 34-year-old Caucasian male who died in the cardiac intensive care unit is shown on the slide below.



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His father died of a heart attack at the age of 40. Assuming this patient's disease had a genetic basis, poor receptor expression in which of the following organs is most likely responsible for his condition?

A Small intestine

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His father died of a heart attack at the age of 40. Assuming this patient's disease had a genetic basis, poor receptor expression in which of the following organs is most likely responsible for his condition?

A. Small intestine
B. Kidney
C. Liver
D. Heart
E. Lung
F. Pancreas

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His father died of a heart attack at the age of 40. Assuming this patient's disease had a genetic basis, poor receptor expression in which of the following organs is most likely responsible for his condition?

- A. Small intestine (3%)
- B. Kidney (2%)
- ✓ C. Liver (87%)
- D. Heart (3%)
- E. Lung (1%)
- F. Pancreas (2%)

Correct

87%

45 secs

01/30/2021

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This patient's right coronary artery (RCA) shows significant occlusion by a large atheromatous plaque with a soft, yellow, lipid core composed mainly of cholesterol and cholesterol esters. Presumably, this patient died from a complication of advanced atherosclerosis, such as a myocardial infarction. His father's similar fate at a young age suggests a familial condition, most likely familial hypercholesterolemia. Familial hypercholesterolemia is one of the most common inherited disorders, and results from autosomal dominant mutations of the LDL receptor gene.

The liver LDL receptor is normally the greatest contributor to the removal of cholesterol-containing IDL and LDL particles from the circulation. Although numerous other cell types, including smooth muscle cells, adrenocortical cells, fibroblasts, and lymphocytes also express high-affinity LDL receptors, approximately 70% of the plasma LDL is normally cleared by the liver. Heterozygotes with one mutant LDL receptor gene have a 2- to 3-fold elevation of plasma cholesterol from birth, due to reduced hepatic IDL and LDL uptake. Homozygotes may have a 5- to 6-fold elevation. In both heterozygotes and homozygotes, the progression of atherosclerosis with aging is accelerated. Complications include coronary artery disease at an unusually young age, as was the case for the patient in the vignette.

(Choices A, B, D, E and F) Although many cell types express the LDL receptor, their rate of LDL uptake from the circulation is usually less than that of hepatocytes. The liver is also the major site of cholesterol

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have a 2- to 3-fold elevation of plasma cholesterol from birth, due to reduced hepatic IDL and LDL uptake. Homozygotes may have a 5- to 6-fold elevation. In both heterozygotes and homozygotes, the progression of atherosclerosis with aging is accelerated. Complications include coronary artery disease at an unusually young age, as was the case for the patient in the vignette.

(Choices A, B, D, E and F) Although many cell types express the LDL receptor, their rate of LDL uptake from the circulation is usually less than that of hepatocytes. The liver is also the major site of cholesterol catabolism and excretion, making it the most important organ in serum cholesterol level homeostasis.

Educational Objective:
Familial hypercholesterolemia, one of the most common autosomal dominant disorders, is the result of heterozygous or homozygous LDL receptor gene mutations, which cause hepatocyte under-expression of functional LDL receptors. This condition can lead to accelerated atherosclerosis and early-onset coronary artery disease.

Pathology	Endocrine, Diabetes & Metabolism	Atherosclerosis
Subject	System	Topic

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A newborn boy is found to have a serum TSH above and serum thyroxine below the normal range for his age. The patient was born at 39 weeks gestation via spontaneous vaginal delivery. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital abnormalities. Ultrasound of the neck shows a normal-sized thyroid gland in the appropriate location. Which of the following is the most likely cause of this patient's condition?

A. Central hypothyroidism
B. Generalized resistance to thyroid hormones
C. Thyroid gland resistance to TSH
D. Thyroid hormone–binding globulin deficiency
E. TSH receptor–stimulating antibodies

Submit

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A newborn boy is found to have a serum TSH above and serum thyroxine below the normal range for his age. The patient was born at 39 weeks gestation via spontaneous vaginal delivery. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital abnormalities. Ultrasound of the neck shows a normal-sized thyroid gland in the appropriate location. Which of the following is the most likely cause of this patient's condition?

A. Central hypothyroidism (10%)
B. Generalized resistance to thyroid hormones (4%)
C. Thyroid gland resistance to TSH (61%)
D. Thyroid hormone–binding globulin deficiency (18%)
E. TSH receptor–stimulating antibodies (5%)

Correct

61%
Answered correctly

01 min, 30 secs
Time Spent

09/18/2020
Last Updated

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Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ◦ Thyroid dysgenesis ◦ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓
• Transient due to maternal exposure ◦ Iodine excess or deficiency ◦ TSH receptor–blocking antibodies ◦ Antithyroid medications	↓	↑

T4 = thyroxine.

This patient has an **elevated serum TSH** and **decreased thyroxine (T4) level**, findings consistent with

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T4 = thyroxine.

This patient has an **elevated serum TSH** and **decreased thyroxine (T4) level**, findings consistent with **primary hypothyroidism**. The most common congenital causes are thyroid dysgenesis (eg, ectopy, hypoplasia) and TSH resistance. Less common, transient etiologies are usually due to maternal conditions (eg, iodine excess, antithyroid medications). Given that this patient's **thyroid is normal in size and location** and the mother has no medical conditions, the most likely cause is thyroid gland resistance to TSH.

TSH is normally produced by the anterior pituitary and binds to TSH receptors on follicular thyroid cells to stimulate T4 production. In TSH resistance, a **mutation in the TSH receptor gene** leads to thyroid insensitivity to TSH and reduced synthesis of T4. Low T4 leads to positive feedback to the pituitary, further increasing TSH levels.

Newborns are usually asymptomatic due to placentally transferred maternal T4 (although thyroid hormones do not readily cross the placenta, enough T4 can usually cross to prevent development of overt symptoms); diagnosis is typically via newborn screening. Treatment is lifelong levothyroxine.

(Choice A) Central hypothyroidism (eg, panhypopituitarism) causes low serum T4 due to decreased production of TSH by the anterior pituitary. This patient's elevated TSH is inconsistent with central

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diagnosis is typically via newborn screening. Treatment is lifelong levothyroxine.

(Choice A) Central hypothyroidism (eg, panhypopituitarism) causes low serum T4 due to decreased production of TSH by the anterior pituitary. This patient's elevated TSH is inconsistent with central hypothyroidism.

(Choice B) Generalized resistance to thyroid hormones due to a thyroid hormone–receptor mutation may lead to hypothyroidism due to insensitivity to T4. However, this condition causes elevated T4 and TSH.

(Choice D) Thyroid hormone–binding globulin deficiency is a benign, euthyroid state characterized by a low total T4 but normal free T4 and TSH levels.

(Choice E) Transplacental transfer of TSH receptor–stimulating antibodies in a mother with Graves disease can cause transient neonatal hyperthyroidism (neonatal Graves disease). Neonatal symptoms include tachycardia and irritability, and laboratory evaluation would show high T4 and low TSH.

Educational objective:
TSH resistance due to a mutation in the TSH receptor gene presents with congenital hypothyroidism, which is characterized by increased TSH and low thyroxine. The thyroid gland is normal in size and location.

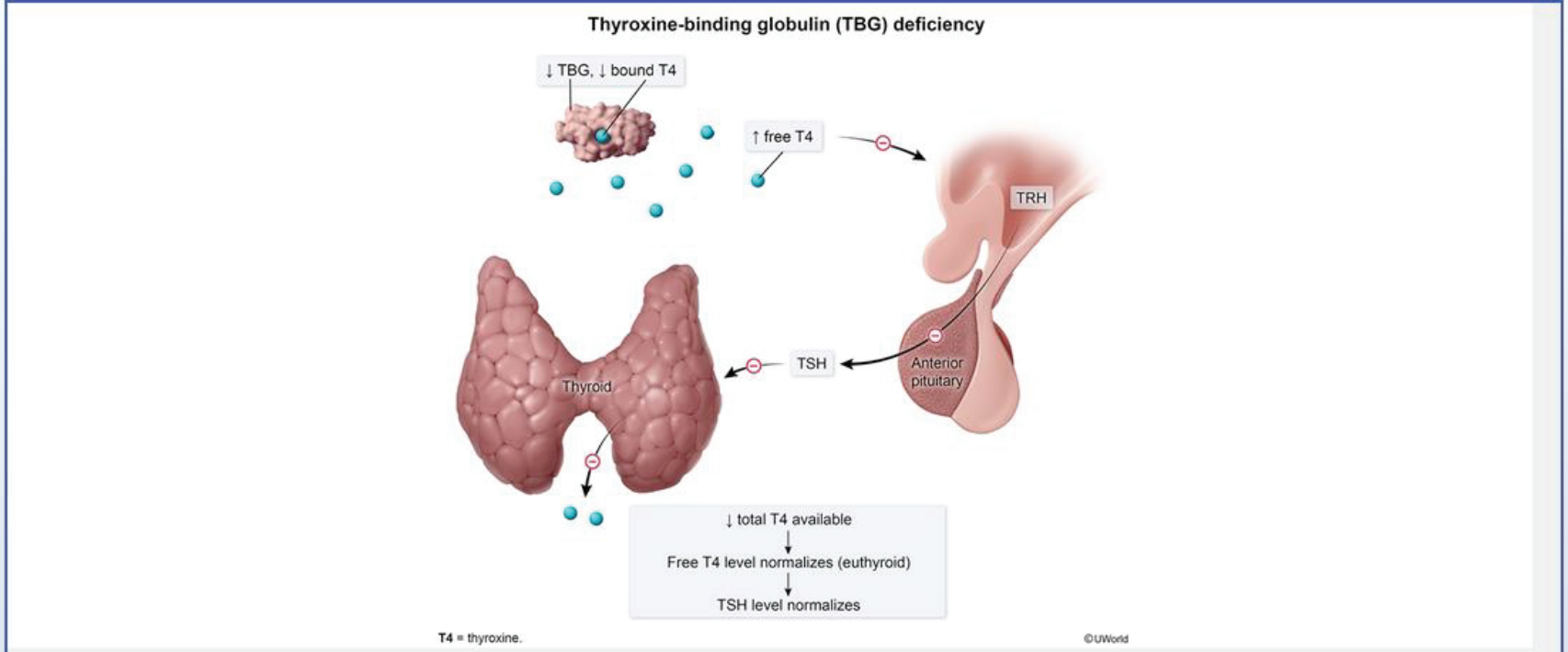
Physiology Endocrine, Diabetes & Metabolism Hypothyroidism

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diagnosis is typically via newborn screening. Treatment is lifelong levothyroxine.

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A 23-year-old man is brought to the emergency department by his roommate due to progressive weakness and confusion. The roommate says that the patient has been "drinking water all of the time and using the bathroom constantly" since he got sick with a cold 2 days ago. Temperature is 37.8 C (100 F), blood pressure is 96/58 mm Hg, and pulse is 112/min. Physical examination shows dry mucous membranes and his urine has a strong, fruity odor. Laboratory results are as follows:

Serum chemistry

Sodium	134 mEq/L
Potassium	3.8 mEq/L
Chloride	100 mEq/L
Bicarbonate	14 mEq/L
Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17

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Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17
$PaCO_2$	40 mm Hg

Based on the current laboratory findings, which of the following is most likely occurring in this patient?

A. Adrenal insufficiency
B. Increased renal bicarbonate loss
C. Low plasma renin activity
D. Renal tubular necrosis
E. Respiratory failure

Submit

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Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17
$PaCO_2$	40 mm Hg

Based on the current laboratory findings, which of the following is most likely occurring in this patient?

A. Adrenal insufficiency (9%)
B. Increased renal bicarbonate loss (49%)
C. Low plasma renin activity (5%)
D. Renal tubular necrosis (9%)
E. Respiratory failure (25%)

Correct
25%
02 mins, 34 secs
10/03/2020

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Appropriate compensatory $PaCO_2$ or bicarbonate changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2$ = (1.5 × bicarbonate) + 8 ± 2 (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in bicarbonate
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in bicarbonate per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in bicarbonate per 10 mm Hg ↓ in $PaCO_2$

*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ and bicarbonate should be considered 40 mm Hg and 24 mEq/L, respectively.

The combination of acute-onset polyuria, polydipsia, volume depletion, and a fruity odor to the urine or

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considered 40 mm Hg and 24 mEq/L, respectively.

The combination of acute-onset polyuria, polydipsia, volume depletion, and a fruity odor to the urine or breath is suggestive of **diabetic ketoacidosis**, which in this patient was most likely precipitated by a viral infection. The laboratory findings of **hyperglycemia** and anion gap metabolic acidosis confirm the diagnosis. The high anion gap is due to the presence of unmeasured anionic ketoacids (eg, beta-hydroxybutyrate, acetoacetate).

Patients with metabolic acidosis usually develop a **compensatory respiratory alkalosis** by hyperventilating (eg, Kussmaul respirations), which helps mitigate the acidemia by causing a drop in the $PaCO_2$. However, if the $PaCO_2$ persists above the expected compensatory range (given by Winter formula, where $PaCO_2 = [1.5 * HCO_3^-] + 8 \pm 2$), it indicates a superimposed respiratory acidosis that is interfering with normal respiratory compensation.

This patient's serum HCO_3^- of 14 mEq/L should be compensated by a $PaCO_2$ in the range of 27-31 mm Hg. However, his **$PaCO_2$ is higher than expected**, indicating that he has a mixed acid-base disturbance consisting of metabolic and respiratory acidoses. Severe diabetic ketoacidosis can cause pulmonary edema, respiratory fatigue, and decreased mental status, which may lead to hypoventilation and subsequent hypercarbic **respiratory failure**.

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subsequent hypercarbic **respiratory failure**.

(Choice A) Acute adrenal insufficiency is characterized by mineralocorticoid deficiency, which can result in hypotension, hyperkalemia, and mild hyperchloremic acidosis. This patient's laboratory findings are not consistent with acute adrenal insufficiency.

(Choice B) Ketoacidosis results in a low serum pH that causes much of the serum bicarbonate (HCO_3^-) to be converted into carbonic acid (H_2CO_3), reducing the amount of bicarbonate filtered by the kidney. In addition, acidosis increases renal tubular H^+ secretion, which promotes bicarbonate reuptake and further reduces renal bicarbonate loss.

(Choice C) This patient's volume depletion and resulting hypotension reduce renal perfusion pressure, leading to increased renin release by the renal juxtaglomerular cells.

(Choice D) Acute tubular necrosis is characterized by progressively increasing serum creatinine with epithelial cell casts and muddy brown granular casts seen on urinalysis. Acute tubular necrosis is unlikely in this patient with normal serum creatinine.

Educational objective:
Normally, metabolic acidosis is partially compensated for by respiratory alkalosis. When the steady-state

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be converted into carbonic acid (H_2CO_3), reducing the amount of bicarbonate filtered by the kidney. In addition, acidosis increases renal tubular H^+ secretion, which promotes bicarbonate reuptake and further reduces renal bicarbonate loss.

(Choice C) This patient's volume depletion and resulting hypotension reduce renal perfusion pressure, leading to increased renin release by the renal juxtaglomerular cells.

(Choice D) Acute tubular necrosis is characterized by progressively increasing serum creatinine with epithelial cell casts and muddy brown granular casts seen on urinalysis. Acute tubular necrosis is unlikely in this patient with normal serum creatinine.

Educational objective:

Normally, metabolic acidosis is partially compensated for by respiratory alkalosis. When the steady-state $PaCO_2$ persists above the range given by the Winter formula ($PaCO_2 = [1.5 * HCO_3^-] + 8 \pm 2$), the patient has a superimposed respiratory acidosis (respiratory failure).

References

- Respiratory failure in diabetic ketoacidosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Metabolic acidosis

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A 72-year-old man is hospitalized for cough, purulent sputum, and shortness of breath. His medical conditions include type 2 diabetes and hypertension. A chest x-ray reveals right lower lobe pneumonia, and treatment is started with supplemental oxygen and antibiotics. While hospitalized, the patient develops persistent sinus tachycardia. Thyroid function tests ordered during the subsequent work up reveal:

Thyroid-stimulating hormone (TSH)	1.3 mU/L (normal: 0.5-5.0 mU/L)
Free thyroxine (T4)	1.2 ng/dL (normal: 0.9-2.4 ng/dL)
Triiodothyronine (T3), total	60 ng/dL (normal: 115-190 ng/dL)

Which of the following is the primary contributor to the decreased total T3 level in this patient?

A. Decreased conversion of T4 to T3 in peripheral tissue
B. Decreased iodination of thyroglobulin
C. Decreased T3 production in the thyroid gland
D. Iodine deficiency
E. Pituitary resistance to thyrotropin-releasing hormone

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and treatment is started with supplemental oxygen and antibiotics. While hospitalized, the patient develops persistent sinus tachycardia. Thyroid function tests ordered during the subsequent work up reveal:

Thyroid-stimulating hormone (TSH)	1.3 mU/L (normal: 0.5-5.0 mU/L)
Free thyroxine (T4)	1.2 ng/dL (normal: 0.9-2.4 ng/dL)
Triiodothyronine (T3), total	60 ng/dL (normal: 115-190 ng/dL)

Which of the following is the primary contributor to the decreased total T3 level in this patient?

- A. Decreased conversion of T4 to T3 in peripheral tissue (86%)
- B. Decreased iodination of thyroglobulin (5%)
- C. Decreased T3 production in the thyroid gland (4%)
- D. Iodine deficiency (2%)
- E. Pituitary resistance to thyrotropin-releasing hormone (1%)

Correct

86%

01 min, 43 secs

01/18/2021

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Explanation

Euthyroid sick syndrome (low T3 syndrome)	
Clinical presentation	• Abnormal thyroid function tests in acutely ill patient • Mild central hypothyroid state; asymptomatic
Pathophysiology	• Suppression of 5'-deiodinase by glucocorticoids and inflammatory cytokines (eg, TNF-alpha, IL-1, IFN-beta) • Decreased peripheral conversion of T4 to T3 • Decreased hypothalamic TRH secretion
Diagnostic testing	• Early: Low T3, normal TSH & T4 • Late: Low T3, TSH & T4

IFN = interferon; **IL** = interleukin; **TNF** = tumor necrosis factor; **TRH** = thyrotropin-releasing hormone.

This patient has **euthyroid sick syndrome** (ESS) (also known as low T3 syndrome), characterized by a

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IFN = interferon; **IL** = interleukin; **TNF** = tumor necrosis factor; **TRH** = thyrotropin-releasing hormone.

This patient has **euthyroid sick syndrome** (ESS) (also known as low T3 syndrome), characterized by a **low T3 level**, normal thyroid-stimulating hormone (TSH), and normal T4. Thyroid hormone is released primarily in the form of T4, with conversion to T3 (the more active form) by 5'-deiodinase (types I and II) in peripheral tissues. In **severe illness**, high levels of cortisol, inflammatory cytokines, and free fatty acids **suppress deiodination of T4**, resulting in lower circulating levels of T3. Concurrently, upregulation of 5'-deiodinase type III leads to increased conversion of T4 to reverse T3 (inactive form).

ESS is thought to be a form of **mild, transient central hypothyroidism**, intended to **decrease maladaptive catabolism** in severe illness; treatment with exogenous thyroid hormone does not improve outcomes and is not indicated. With increasing duration and severity of illness, central production of thyrotropin-releasing hormone (TRH) and TSH are also suppressed, leading to lower circulating TSH and T4 levels.

(Choice B) Thyroglobulin is iodinated by thyroperoxidase (TPO) in follicular colloid. TPO activity is increased by TSH and suppressed by thioamides (eg, methimazole, propylthiouracil). Although TSH (and therefore iodination of thyroglobulin) falls in later ESS, this patient's TSH is normal, and his normal T4 level suggests adequate iodination.

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(Choice B) Thyroglobulin is iodinated by thyroperoxidase (TPO) in follicular colloid. TPO activity is increased by TSH and suppressed by thioamides (eg, methimazole, propylthiouracil). Although TSH (and therefore iodination of thyroglobulin) falls in later ESS, this patient's TSH is normal, and his normal T4 level suggests adequate iodination.

(Choice C) Although a small amount of T3 is produced in the thyroid (from T4 via 5'-deiodinase type II), most is produced in peripheral tissues. The fall in circulating T3 levels in ESS is primarily due to suppression of peripheral conversion.

(Choice D) Iodine deficiency is rare in developed countries. When it occurs, it presents chronically with goiter and primary hypothyroidism (ie, elevated TSH, low T4). This patient has a normal TSH level, making iodine deficiency unlikely.

(Choice E) Proinflammatory cytokines decrease TSH levels by reducing secretion of TRH in the hypothalamus. In patients with ESS, TSH increases normally following administration of exogenous TRH, suggesting an intact pituitary response to TRH.

Educational objective:
Euthyroid sick syndrome (ESS) is a common pattern of thyroid function markers seen in severely ill

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suggests adequate iodination.

(Choice C) Although a small amount of T3 is produced in the thyroid (from T4 via 5'-deiodinase type II), most is produced in peripheral tissues. The fall in circulating T3 levels in ESS is primarily due to suppression of peripheral conversion.

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(Choice E) Proinflammatory cytokines decrease TSH levels by reducing secretion of TRH in the hypothalamus. In patients with ESS, TSH increases normally following administration of exogenous TRH, suggesting an intact pituitary response to TRH.

Educational objective:
Euthyroid sick syndrome (ESS) is a common pattern of thyroid function markers seen in severely ill patients. It is characterized by decreased conversion of T4 to T3 in peripheral tissues. Initial findings include a low T3 level, but later, T4 and thyroid-stimulating hormone levels may also decrease. ESS may represent a mild central hypothyroid state, which functions to minimize catabolism in severe illness.

Physiology Endocrine, Diabetes & Metabolism Euthyroid sick syndrome

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A 53-year-old man comes to the office due to uncontrolled type 2 diabetes mellitus. Three years ago, the patient was diagnosed with diabetes and started on metformin and lifestyle modification. In the past year, his hemoglobin A1c level has been steadily rising. Blood pressure is 145/90 mm Hg. BMI is 37 kg/m^2. Laboratory results are normal except for a fasting plasma glucose of 155 mg/dL and a hemoglobin A1c level of 8%. Additional treatment with canagliflozin is initiated. Over the next several days, which of the following changes are most likely to occur in this patient due to the new medication?

	Urinary glucose excretion	Total body sodium content	Extracellular fluid volume
A.	Decreased	Decreased	Unchanged
B.	Decreased	Increased	Decreased
C.	Increased	Decreased	Decreased
D.	Increased	Unchanged	Increased
E.	Increased	Increased	Decreased

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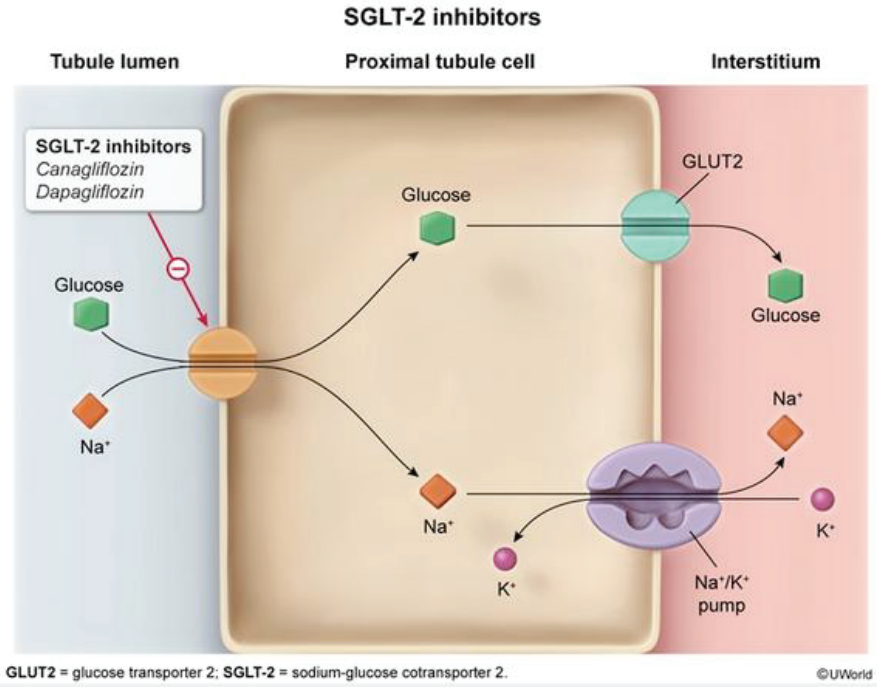
patient was diagnosed with diabetes and started on metformin and lifestyle modification. In the past year, his hemoglobin A1c level has been steadily rising. Blood pressure is 145/90 mm Hg. BMI is 37 kg/m^2. Laboratory results are normal except for a fasting plasma glucose of 155 mg/dL and a hemoglobin A1c level of 8%. Additional treatment with canagliflozin is initiated. Over the next several days, which of the following changes are most likely to occur in this patient due to the new medication?

		Urinary glucose excretion	Total body sodium content	Extracellular fluid volume	
	A.	~~Decreased~~	~~Decreased~~	~~Unchanged~~	(1%)
	B.	~~Decreased~~	~~Increased~~	~~Decreased~~	(1%)
✓	C.	Increased	Decreased	Decreased	(74%)
✗	D.	Increased	Unchanged	Increased	(8%)
	E.	~~Increased~~	~~Increased~~	~~Decreased~~	(14%)

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Explanation

Exhibit Display



GLUT2 = glucose transporter 2; SGLT-2 = sodium-glucose cotransporter 2.

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GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

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Sodium-glucose cotransporter 2 (SGLT2) is a low-affinity, high-capacity transport protein that is responsible for reabsorbing 90% of filtered glucose in the proximal renal tubule. Glucose reabsorption by SGLT2 is driven by cotransport of sodium, which occurs down its concentration gradient. The sodium is actively pumped across the basolateral membrane by Na-K-ATPase, and glucose follows by facilitated diffusion via glucose transporter-2.

SGLT2 inhibitors (eg, canagliflozin, dapagliflozin) are oral antidiabetic agents that have the following effects:

- Decreased renal reabsorption of glucose, leading to **increased urinary glucose excretion** and lower blood glucose levels
- **Natriuresis** and **osmotic diuresis** due to decreased reabsorption of sodium and glucose, leading to a small **decrease in extracellular fluid volume**, total **body sodium content**, and blood pressure
- Decreased sodium reabsorption and increased sodium delivery to the macula densa, leading to decreased activation of the renin-angiotensin-aldosterone system, lower glomerular (and systemic) pressures, and delayed progression of nephropathy

Educational objective:

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- **Natriuresis** and **osmotic diuresis** due to decreased reabsorption of sodium and glucose, leading to a small **decrease in extracellular fluid volume**, total **body sodium content**, and blood pressure
- Decreased sodium reabsorption and increased sodium delivery to the macula densa, leading to decreased activation of the renin-angiotensin-aldosterone system, lower glomerular (and systemic) pressures, and delayed progression of nephropathy

Educational objective:

Sodium-glucose cotransporter 2 inhibitors decrease renal reabsorption of glucose and sodium, leading to increased urinary glucose excretion and decreased blood glucose levels. In addition, natriuresis and osmotic diuresis lead to a small decrease in extracellular fluid volume, total body sodium content, and blood pressure.

References

- SGLT2 inhibitors with cardiovascular benefits: transforming clinical care in type 2 diabetes mellitus.

Pharmacology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 16-year-old boy is brought to the office for evaluation of irritability, slow growth, and acne. The patient plays soccer and has been following an aggressive strength-training program. When asked, he admits to using a performance-enhancing substance for the past 6 months. What additional findings would most likely be present in this patient now compared to 6 months ago?

	Serum LH	Serum estrogen	Spermatogenesis
A.	High	High	High
B.	High	High	Low
C.	High	Low	Low
D.	Low	High	High
E.	Low	High	Low
F.	Low	Low	Low

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plays soccer and has been following an aggressive strength-training program. When asked, he admits to using a performance-enhancing substance for the past 6 months. What additional findings would most likely be present in this patient now compared to 6 months ago?

	Serum LH	Serum estrogen	Spermatogenesis	
A.	~~High~~	~~High~~	~~High~~	(1%)
B.	~~High~~	~~High~~	~~Low~~	(8%)
C.	~~High~~	~~Low~~	~~Low~~	(4%)
D.	~~Low~~	~~High~~	~~High~~	(4%)
✓ E.	Low	High	Low	(62%)
F.	Low	Low	Low	(17%)

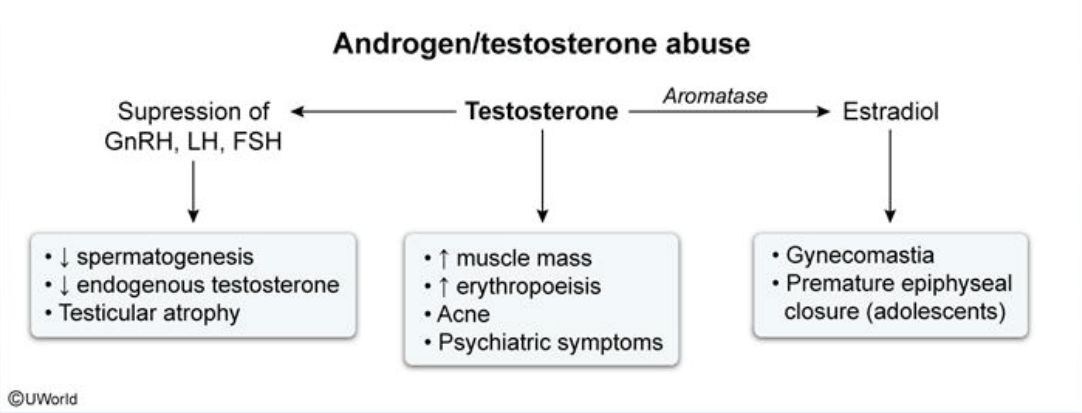
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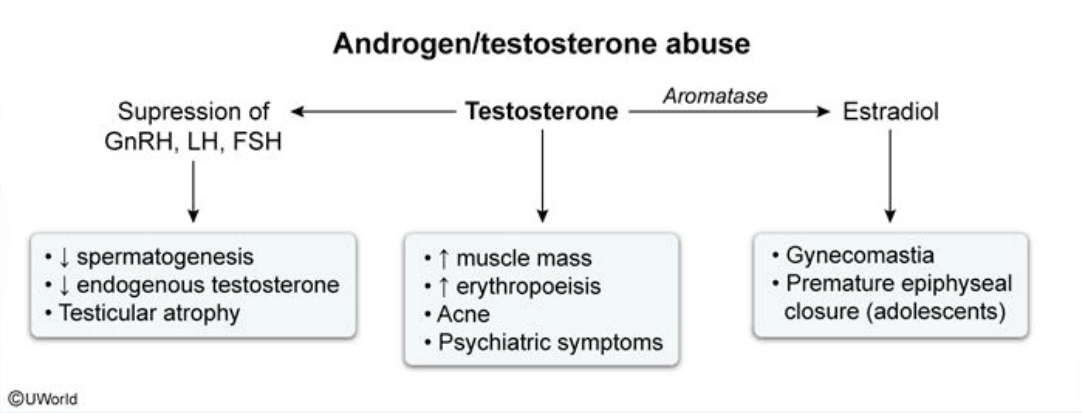
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Testosterone stimulates increased protein synthesis by skeletal myocytes. Some competitive athletes and body builders **abuse testosterone** and other exogenous androgens to increase muscle mass and improve athletic performance. However, excessive androgenic activity can cause significant adverse effects, including **acne** (increased dermal sebum production) and neuropsychiatric changes (eg, **irritability, aggression**, and anxiety).

Androgen abuse can also result in profound endocrine and reproductive effects. Spermatogenesis in the seminiferous tubules is driven by FSH and requires a high local concentration of testosterone, which is produced by nearby Leydig cells and retained by androgen-binding protein. Exogenous androgens

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Androgen abuse can also result in profound endocrine and reproductive effects. Spermatogenesis in the seminiferous tubules is driven by FSH and requires a high local concentration of testosterone, which is produced by nearby Leydig cells and retained by androgen-binding protein. Exogenous androgens suppress GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, **impaired spermatogenesis (Choice D)**, and **testicular atrophy**.

In addition, excess testosterone is converted by aromatase to yield high levels of estradiol **(Choice F)**, which can lead to **gynecomastia**. In adolescent users, high circulating estrogen levels can also cause **premature epiphyseal closure** and short stature.

(Choices A, B, and C) Excess circulating exogenous androgens (eg, testosterone) suppress pituitary LH release.

Educational objective:

Androgen abuse suppresses GnRH, LH, and FSH secretion, leading to reduced endogenous testosterone secretion, impaired spermatogenesis, and testicular atrophy. In addition, excess testosterone is converted by aromatase to estradiol, which can lead to gynecomastia.

References

- Performance-enhancing drug use in adolescence.

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A 34-year-old man comes to the office with his girlfriend for follow-up of type 1 diabetes mellitus. He was diagnosed 15 years ago and is currently treated with a combination of basal and rapid-acting insulin injections. The patient has been experiencing intermittent episodes of hypoglycemia with a blood glucose of 35-54 mg/dL. Two weeks ago, he was taken to the emergency department after passing out due to low glucose levels. The patient is prescribed an injectable medication to be administered at home by a caregiver when hypoglycemia is associated with impaired consciousness. This medication rapidly improves hypoglycemia by which of the following mechanisms?

A. Decreasing uptake of glucose by fat and muscles
B. Decreasing uptake of glucose by the liver
C. Increasing gastrointestinal absorption of glucose
D. Increasing gluconeogenesis
E. Increasing glycogenolysis

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A. Decreasing uptake of glucose by fat and muscles (10%)
B. Decreasing uptake of glucose by the liver (6%)
C. Increasing gastrointestinal absorption of glucose (3%)
D. Increasing gluconeogenesis (34%)
E. Increasing glycogenolysis (46%)

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Metabolic effects of glucagon	
Liver	• ↑ glycogenolysis (primary) • ↑ gluconeogenesis, ↓ glycolysis (secondary) • ↓ lipogenesis
Adipose	• ↑ lipolysis
Heart	• ↑ heart rate, contractility (high dose) • Useful in treating beta blocker overdose

Hypoglycemia initially manifests with neurogenic (autonomic) symptoms, including anxiety, tremor, and sweating. However, as hypoglycemia worsens patients may develop life-threatening neuroglycopenic symptoms, including confusion, **loss of consciousness**, and seizures. Mild to moderate hypoglycemia is usually self-treated with oral fast-acting carbohydrates (eg, glucose tablets, fruit juices). However, when hypoglycemia becomes severe enough to induce unconsciousness, **parenteral treatment** is necessary.

In a medical setting, severe hypoglycemia is usually treated with an infusion of glucose, but this requires intravenous access. In a nonmedical setting, severe hypoglycemia can be treated with **emergency**

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hypoglycemia becomes severe enough to induce unconsciousness, **parenteral treatment** is necessary.

In a medical setting, severe hypoglycemia is usually treated with an infusion of glucose, but this requires intravenous access. In a nonmedical setting, severe hypoglycemia can be treated with **emergency glucagon kits**, which are produced in intranasal and subcutaneous/intramuscular formulations and can be administered by a caregiver or informed bystander.

Glucagon rapidly corrects hypoglycemia by **increasing hepatic glycogenolysis**; the free glucose residues are then released into the blood, causing a return to consciousness within 10-15 minutes of administration. Subsequently, glucagon induces gluconeogenesis and suppresses hepatic glucose uptake, which provide a delayed but somewhat more sustained effect **(Choices B and D)**.

(Choice A) Glucagon has little direct effect on glucose uptake in adipose and muscle tissue, which is primarily regulated by insulin. Although epinephrine raises blood glucose (in part) by suppression of peripheral glucose uptake and can be administered by auto-injector, it is less effective than glucagon for hypoglycemia and is primarily used for severe allergy/anaphylaxis.

(Choice C) Glucose is taken up from the intestinal lumen into epithelial cells via sodium-glucose cotransporter-1 (SGLT-1) and then passed into the blood via glucose transporter 2 (GLUT-2). Glucagon causes a decrease in intestinal motility but does not have a major effect on the transport of glucose by SGLT-1 or GLUT-2

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which provide a delayed but somewhat more sustained effect **(Choices B and D)**.

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Educational objective:

Severe hypoglycemia causing impaired conciousness can be treated by a caregiver or bystander with injectable or intranasal glucagon. Glucagon rapidly corrects hypoglycemia by increasing hepatic glycogenolysis, resulting in the release of glucose from preexisting hepatic glycogen stores.

References

- Novel preparations of glucagon for the prevention and treatment of hypoglycemia.

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A 67-year-old man comes to the office due to increased fatigue and weight gain over the past 6 months. He has hypertension controlled with a calcium channel blocker. Two years ago, the patient's physical examination was unremarkable, and his blood tests, including a lipid panel, were normal. Blood pressure is 135/98 mm Hg, and pulse is 62/min. BMI is 28 kg/m^2. On physical examination, the thyroid appears to be mildly enlarged and is irregular and firm in consistency. Laboratory studies reveal elevated TSH, low free thyroxine (T4), high total and LDL cholesterol, and mildly elevated triglyceride levels. Which of the following is the most likely underlying mechanism for the elevated cholesterol in this patient?

A. Activation of transcription factor peroxisome proliferator–activated receptor alpha
B. Decreased LDL receptor gene expression
C. Increased lipoprotein lipase gene expression
D. Induction of HMG-CoA reductase
E. Upregulation of LDL receptor degradation

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A. ~~Activation of transcription factor peroxisome proliferator–activated receptor alpha~~ (9%)

✓ B. Decreased LDL receptor gene expression (57%)

C. ~~Increased lipoprotein lipase gene expression~~ (7%)

D. ~~Induction of HMG-CoA reductase~~ (13%)

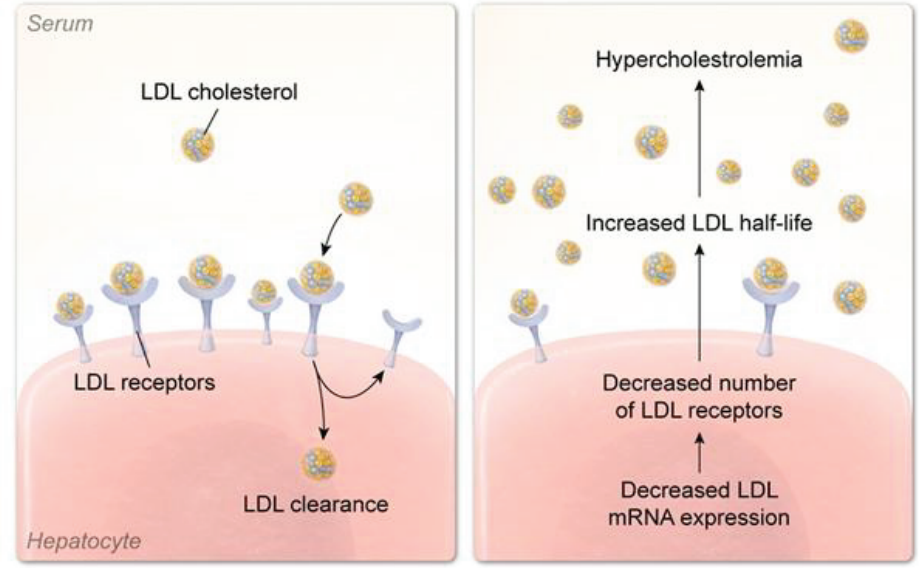
E. Upregulation of LDL receptor degradation (11%)

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Hypothyroidism effect on lipids



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This patient has primary hypothyroidism presenting with fatigue, weight gain, and goiter, along with elevated TSH and low free thyroxine (T4) levels. **Hypothyroidism** can cause a number of adverse effects on serum lipids, including elevating total cholesterol, LDL cholesterol, and triglyceride levels.

Hypothyroidism causes **decreased LDL receptor expression**, leading to decreased clearance of LDL with resultant **increased blood LDL** levels. Hypothyroidism may also decrease LDL receptor activity and biliary excretion of cholesterol. Hypertriglyceridemia can occur in hypothyroidism due to decreased expression of lipoprotein lipase **(Choice C)**. Along with effects on blood pressure (eg, hypertension due to increased peripheral vascular resistance), the adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

(Choice A) Peroxisome proliferator–activated receptor alpha (PPAR-α) stimulates fatty-acid uptake and beta oxidation; increased PPAR-α expression would cause a reduction in triglyceride levels. Decreased PPAR-α activity leads to hypertriglyceridemia and lipid accumulation within the liver (fatty liver disease) but is not associated with hypothyroidism.

(Choice D) Hypothyroidism is associated with decreased activity of HMG-CoA reductase and therefore decreased de novo synthesis of cholesterol; however, patients still develop hyperlipidemia due to reduced

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beta oxidation; increased PPAR-α expression would cause a reduction in triglyceride levels. Decreased PPAR-α activity leads to hypertriglyceridemia and lipid accumulation within the liver (fatty liver disease) but is not associated with hypothyroidism.

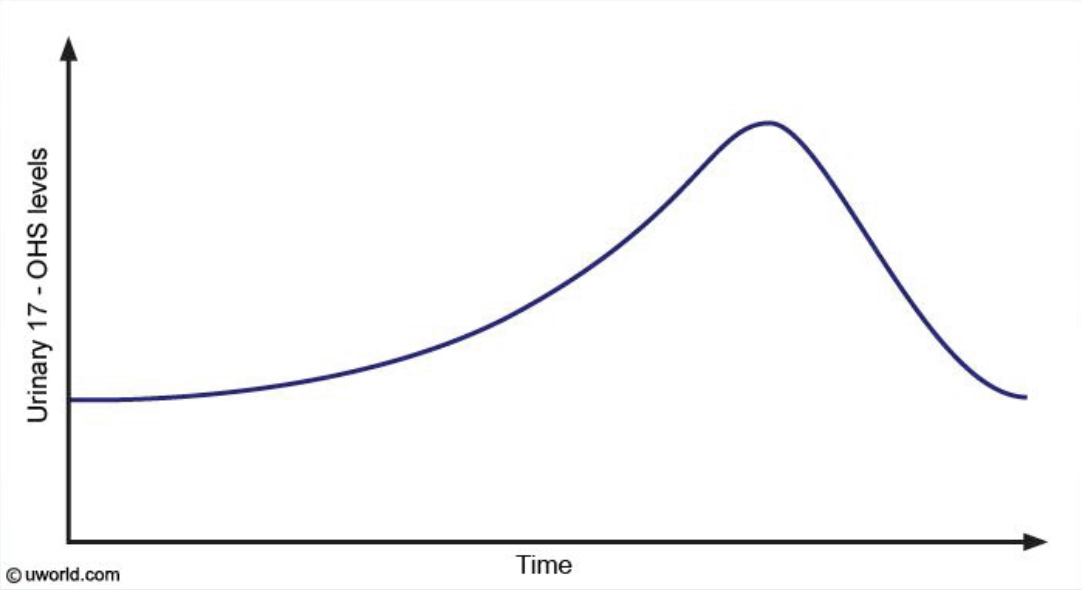
(Choice D) Hypothyroidism is associated with decreased activity of HMG-CoA reductase and therefore decreased de novo synthesis of cholesterol; however, patients still develop hyperlipidemia due to reduced LDL clearance. Thyroid hormone (not hypothyroidism) induces expression of HMG-CoA reductase.

(Choice E) Similar to decreased LDL receptor expression, increased LDL receptor degradation leads to elevated blood LDL levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases the degradation of hepatic LDL receptors; alirocumab, a monoclonal antibody against PCSK9, blocks this effect, leading to a reduction in LDL levels. However, hypothyroidism is not associated with increased LDL receptor degradation.

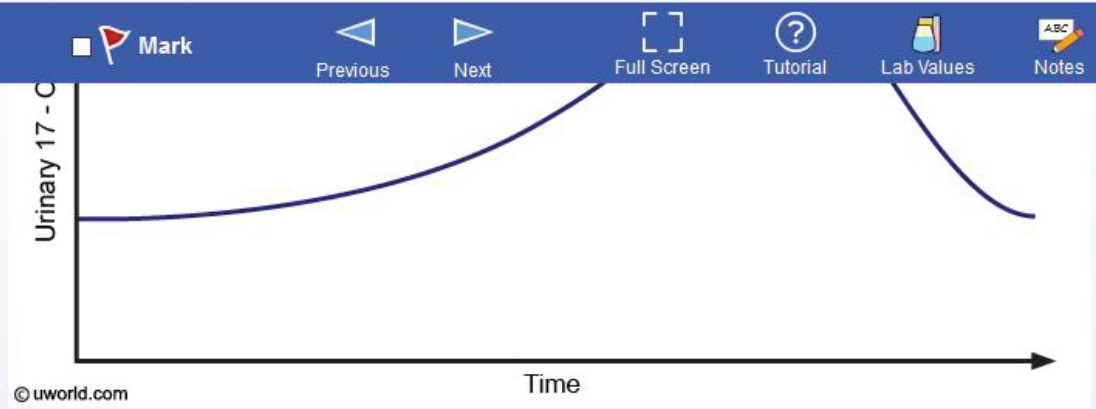
Educational objective:
Hypothyroidism causes decreased expression of LDL receptors in the liver, leading to decreased clearance of LDL and increased blood LDL levels. It also causes hypertriglyceridemia due to decreased expression of lipoprotein lipase. The adverse effects of hypothyroidism on lipid levels can increase the risk of coronary atherosclerosis.

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A 60-year-old woman is being evaluated for chronic weakness and fatigue. She has no other medical problems and takes no medications. After performing initial laboratory studies, the physician decides to proceed with a metyrapone stimulation test. The changes in urinary 17-hydroxycorticosteroid (17-OHS) excretion following metyrapone administration are shown in the graph below.



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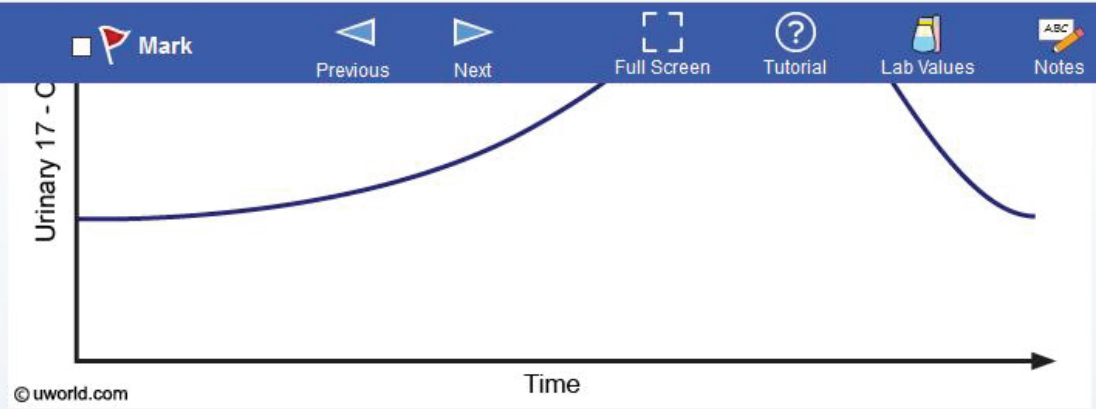


Which of the following mechanisms is most likely responsible for the findings seen in the graph?

A. ACTH surge
B. Aldosterone overproduction
C. Cortisol overproduction
D. Renin surge
E. Vasopressin overproduction

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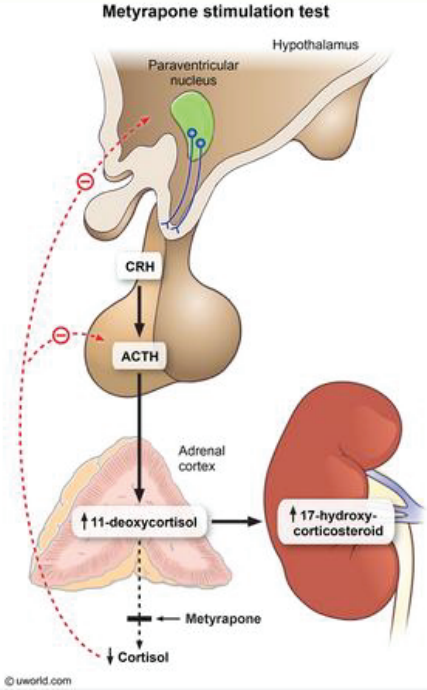
Which of the following mechanisms is most likely responsible for the findings seen in the graph?

- A. ACTH surge (63%)
- B. Aldosterone overproduction (8%)
- C. Cortisol overproduction (23%)
- D. Renin surge (2%)
- E. Vasopressin overproduction (1%)

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Like most hormones, secretion of cortisol is regulated via a negative feedback loop. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus in response to stress and circadian signals received from other parts of the central nervous system. CRH stimulates ACTH release by the pituitary, which in turn increases cortisol secretion by the adrenal cortex. High cortisol levels suppress secretion of ACTH and CRH, and low cortisol levels cause an increase in ACTH and CRH secretion.

Although not commonly used, the **metyrapone stimulation test** is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity. Metyrapone blocks cortisol synthesis by inhibiting **11-β-hydroxylase**, which converts **11-deoxycortisol to cortisol** in the zona fasciculata. Because 11-deoxycortisol lacks glucocorticoid activity, it does not inhibit pituitary ACTH secretion. As a result, the reduction in cortisol levels following metyrapone administration cause an increase in pituitary ACTH secretion. This leads to increased production of 11-deoxycortisol, which is further metabolized by the liver to **17-hydroxycorticosteroids** that accumulate in the urine.

Serum 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels will normally rise in response to metyrapone, indicating an intact HPA axis. Failure of these steroid levels to increase implies primary or secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

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secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

(Choices B and D) The renin-angiotensin-aldosterone system regulates aldosterone synthesis by the zona glomerulosa. Because metyrapone inhibits 11-β-hydroxylase, aldosterone synthesis will decrease. However, accumulation of the aldosterone precursor 11-deoxycorticosterone (a weak mineralocorticoid) prevents the development of mineralocorticoid deficiency, so renin levels will not change significantly.

(Choice C) The inhibition of 11-β-hydroxylase by metyrapone would lead to a decrease in cortisol, not an increase.

(Choice E) Vasopressin is a hormone secreted by the posterior pituitary that is responsible for regulating water balance. Additionally, vasopressin acts as a potentiator for CRH, enhancing the release of ACTH. However, there is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to lead to vasopressin overproduction.

Educational objective:
Administration of metyrapone will cause a decrease in cortisol synthesis via inhibition of 11-β-hydroxylase. In patients with an intact hypothalamic-pituitary-adrenal axis, this will cause a reactive increase in ACTH, 11-deoxycortisol, and urinary 17-hydroxycorticosteroid levels.

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A 22-year-old man comes to the emergency department with abdominal pain and vomiting. His symptoms began acutely 24 hours ago with nausea and decreased appetite. His medical history is unremarkable. The patient drinks 3-4 beers a week and does not use tobacco or illicit drugs. BMI is 37 kg/m^2. Physical examination is notable for moderate epigastric tenderness with decreased bowel sounds but no rebound tenderness, guarding, or abdominal rigidity. Fasting laboratory studies show a serum triglyceride concentration of 1,500 mg/dL (normal: <200 mg/dL). Once the patient has been medically stabilized, which of the following medications would be most helpful in preventing recurrences of his condition?

A. Atorvastatin
B. Cholestyramine
C. Ezetimibe
D. Fenofibrate
E. Niacin
F. Omega-3 fatty acids

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A. Atorvastatin (14%)
B. Cholestyramine (7%)
C. Ezetimibe (6%)
D. Fenofibrate (59%)
E. Niacin (11%)
F. Omega-3 fatty acids (1%)

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Correct answer

59%
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Antihyperlipidemic medications			
Drug	**Mechanism**	**Major lipid effects**	**Side effects**
Statins	• Inhibit HMG-CoA reductase	• ↓↓ **LDL** • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout

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	absorption		
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

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This patient most likely has **acute pancreatitis** due to severe **hypertriglyceridemia**. Small quantities of pancreatic lipase normally leak into the pancreatic capillaries, where they can metabolize triglycerides to **free fatty acids**, which have toxic and inflammatory effects on the pancreas. The risk of pancreatitis rises with increasing triglyceride levels and is most significant when triglycerides are severely elevated (>1,000 mg/dL).

Triglycerides loosely reflect caloric balance; a calorie-restricted diet with increased exercise and reduced alcohol intake can provide a rapid and significant drop in triglyceride levels. Lipid-lowering medications are also indicated for patients with moderate to severe hypertriglyceridemia. **Fibrates** (eg, fenofibrate, gemfibrozil) work by activating peroxisome proliferator-activated receptor-alpha (**PPAR-α**), which increases the synthesis of lipoprotein lipase.

(Choice A) Although statins (eg, atorvastatin) are the preferred lipid-lowering agents for the prevention of cardiovascular disease, they only modestly lower triglyceride levels and would be less effective than fibrates for preventing recurrent pancreatitis due to hypertriglyceridemia.

(Choices B and C) Bile acid-binding resins (eg, cholestyramine) work by binding bile acids in the gastrointestinal tract, subsequently interfering with enterohepatic bile acid circulation. Ezetimibe selectively inhibits intestinal cholesterol absorption. These medications are used primarily for the treatment of

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(Choices B and C) Bile acid-binding resins (eg, cholestyramine) work by binding bile acids in the gastrointestinal tract, subsequently interfering with enterohepatic bile acid circulation. Ezetimibe selectively inhibits intestinal cholesterol absorption. These medications are used primarily for the treatment of hypercholesterolemia.

(Choice E) Niacin decreases hepatic production of VLDLs and reduces triglyceride release from adipose tissue. It has a weaker effect in lowering triglycerides than fibrates and is associated with significant side effects, especially flushing.

(Choice F) Fish oil supplements containing omega-3 fatty acids lower triglyceride levels by decreasing the production of VLDLs. Fish oils decrease serum triglycerides to a lesser degree than fibrates but may be added to fibrates in patients whose triglyceride levels are not adequately controlled with a fibrate alone.

Educational objective:
In patients with severe hypertriglyceridemia, pancreatic lipases can cause toxic levels of free fatty acids to be released within the pancreatic tissue, leading to acute pancreatitis. Fibrates (eg, fenofibrate) are the most effective agents for the treatment of hypertriglyceridemia.

References

- Optimal pharmacologic approach to patients with hypertriglyceridemia and low high-density lipoprotein-

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A 65-year-old man comes to the office due to advanced prostate cancer with bone metastases. For the last 4 months, he has been treated with a GnRH agonist, which has significantly reduced his bone pain. However, the patient now reports discomfort at the anterior chest wall. Physical examination reveals bilateral, mildly tender enlargement of the breast tissue behind the nipple-areolar complex. Early initiation of which of the following medications would be most appropriate for preventing this patient's breast symptoms?

A. Bicalutamide
B. Danazol
C. Finasteride
D. Spironolactone
E. Tamoxifen

Submit

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A 65-year-old man comes to the office due to advanced prostate cancer with bone metastases. For the last 4 months, he has been treated with a GnRH agonist, which has significantly reduced his bone pain. However, the patient now reports discomfort at the anterior chest wall. Physical examination reveals bilateral, mildly tender enlargement of the breast tissue behind the nipple-areolar complex. Early initiation of which of the following medications would be most appropriate for preventing this patient's breast symptoms?

A. Bicalutamide (13%)
B. Danazol (17%)
C. Finasteride (11%)
D. Spironolactone (8%)
✓ E. Tamoxifen (48%)

Correct

48%
Answered correctly

01 min, 37 secs
Time Spent

12/02/2020
Last Updated

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Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis
Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity) • Decreased testosterone levels (eg, chronic kidney disease, hypogonadism) • Medication effect ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole) ◦ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors) ◦ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the development of glandular breast tissue in males. It is characterized by **ductal epithelial hyperplasia** with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that **increase the estrogen to androgen ratio** can lead to gynecomastia. Common pathologic causes include cirrhosis (increased aromatase activity, decreased

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Gynecomastia is the development of glandular breast tissue in males. It is characterized by **ductal epithelial hyperplasia** with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that **increase the estrogen to androgen ratio** can lead to gynecomastia. Common pathologic causes include cirrhosis (increased aromatase activity, decreased clearance of estrogens), end-stage renal disease (decreased testosterone production), and medications (eg, spironolactone, ketoconazole).

Men with prostate cancer who receive **androgen-deprivation therapy** (eg, orchiectomy, long-acting GnRH agonists, androgen receptor inhibitors) can develop gynecomastia due to dramatic (>95%) reductions in circulating testosterone (with lesser reductions in estrogens). Treatment with **tamoxifen**, a selective estrogen receptor modulator that acts as an estrogen antagonist in the breast, can reduce the risk of gynecomastia in these patients.

(Choice A) Bicalutamide is a testosterone receptor antagonist used in the treatment of prostate cancer. This drug can cause or worsen gynecomastia due to the reduced physiologic testosterone effect.

(Choice B) Danazol is a synthetic steroid with androgenic and antiestrogenic effects. It may improve gynecomastia in patients with hypogonadism but can lead to rapid growth of prostate cancer and would not be appropriate for this patient

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(Choice A) Bicalutamide is a testosterone receptor antagonist used in the treatment of prostate cancer. This drug can cause or worsen gynecomastia due to the reduced physiologic testosterone effect.

(Choice B) Danazol is a synthetic steroid with androgenic and antiestrogenic effects. It may improve gynecomastia in patients with hypogonadism but can lead to rapid growth of prostate cancer and would not be appropriate for this patient.

(Choices C and D) Finasteride is a 5-α reductase inhibitor that reduces the conversion of testosterone to dihydrotestosterone; it is used for treatment of benign prostatic hyperplasia and male-pattern hair loss. Spironolactone is an aldosterone antagonist that also decreases testosterone production and inhibits the testosterone receptor; it is commonly used for heart failure, cirrhosis, and hypertension. Both of these agents are associated with increased risk of gynecomastia.

Educational objective:
Gynecomastia is the development of glandular breast tissue in males and is commonly seen in men receiving androgen deprivation therapy for prostate cancer. Tamoxifen inhibits the effect of estrogen on breast tissue and can reduce the risk of gynecomastia in these patients.

Pharmacology	Endocrine, Diabetes & Metabolism	Gynecomastia
Subject	System	Topic

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An 18-year-old man comes to the office due to a progressive skin rash over the past year. He also has a long-standing history of an intermittent burning sensation in his palms and soles that is exacerbated by stress and fatigue. The burning sensation is particularly severe after exercise, during which the patient notes that he sweats minimally. Skin examination shows clusters of non-blanching, red papules in the gluteal, inguinal, and umbilical areas. Laboratory evaluation reveals an undetectable level of α-galactosidase A. Which of the following conditions is this patient at greatest risk for developing?

A. Ataxia
B. Hepatomegaly
C. Neurofibrosarcoma
D. Optic atrophy
E. Renal failure

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A. Ataxia (13%)
B. Hepatomegaly (24%)
C. Neurofibrosarcoma (4%)
D. Optic atrophy (17%)
E. Renal failure (40%)

Correct

40%
Answered correctly

02 mins, 01 sec
Time Spent

01/18/2021
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Fabry disease	
Pathophysiology	• X-linked recessive • α-galactosidase A deficiency results in accumulation of globotriaosylceramide
Clinical features	• Neuropathic pain • Angiokeratomas • Telangiectasias • Glomerular disease (eg, proteinuria) • Cerebrovascular disease (eg, TIA, stroke) • Cardiac disease (eg, left ventricular hypertrophy)

TIA = transient ischemic attack.

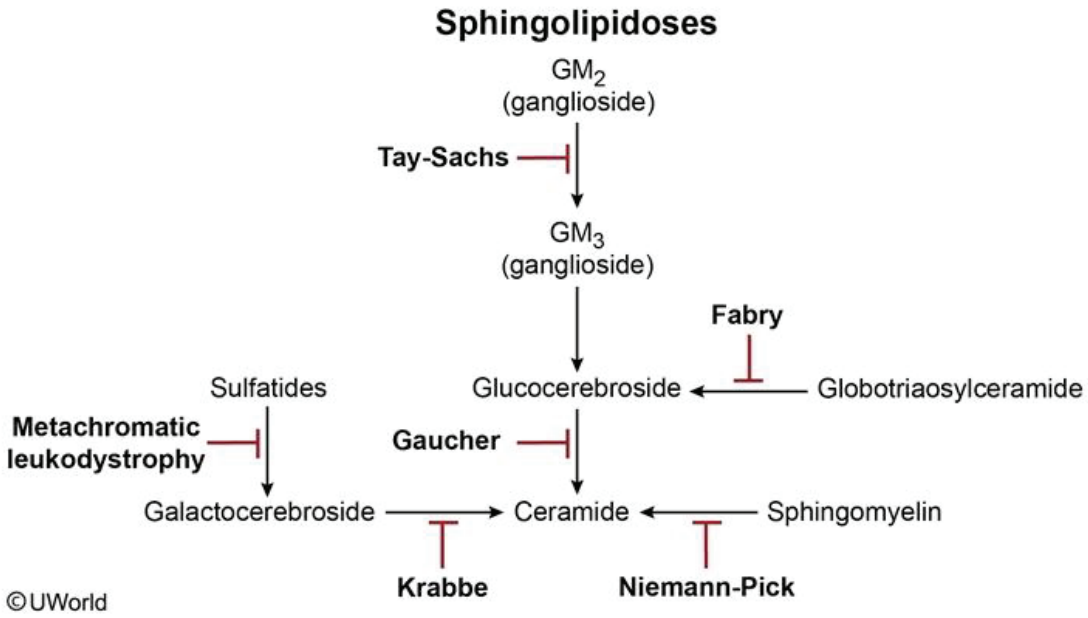
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Fabry disease is an **X-linked recessive** lipid storage disorder characterized by **α-galactosidase A deficiency**. α-galactosidase A is a lysosomal enzyme responsible for the breakdown of **globotriaosylceramide (Gb3)**, a sphingolipid also known as ceramide trihexoside. Gb3 accumulation in vascular smooth muscle cells, glomerular/distal tubule cells, cardiac myocytes, and dorsal root and autonomic ganglia accounts for the adverse manifestations of Fabry disease.

The earliest symptoms present during adolescence and include **neuropathic pain** and **hypohidrosis**

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The earliest symptoms present during adolescence and include **neuropathic pain** and **hypohidrosis**

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Fabry disease is an **X-linked recessive** lipid storage disorder characterized by **α-galactosidase A deficiency**. α-galactosidase A is a lysosomal enzyme responsible for the breakdown of **globotriaosylceramide (Gb3)**, a sphingolipid also known as ceramide trihexoside. Gb3 accumulation in vascular smooth muscle cells, glomerular/distal tubule cells, cardiac myocytes, and dorsal root and autonomic ganglia accounts for the adverse manifestations of Fabry disease.

The earliest symptoms present during adolescence and include **neuropathic pain** and **hypohidrosis** (decreased sweating). Small-fiber nerve involvement results in severe distal extremity pain and burning as well as distal loss of hot/cold temperature sensation. Exacerbating factors include exercise, stress, and fatigue. In late adolescence, **angiokeratomas** and **telangiectasias** develop on the skin. Angiokeratomas are dark red, non-blanching macules and papules that classically occur in clusters over the buttocks, groin, and umbilicus.

In early and mid-adulthood, **cerebrovascular** (eg, transient ischemic attack, stroke) and **cardiac** (eg, left ventricular hypertrophy) diseases develop and are the most common causes of death. In addition, Gb3 buildup in the **glomerulus and distal tubule** results in **proteinuria and polyuria**, respectively, and can progress to **renal failure** in the absence of enzyme replacement therapy.

(Choice A) Accumulation of cerebroside sulfate in metachromatic leukodystrophy (arylsulfatase A

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(Choice A) Accumulation of cerebroside sulfate in metachromatic leukodystrophy (arylsulfatase A deficiency) causes progressive demyelination leading to ataxia, peripheral neuropathy, seizures, and hypotonia.

(Choice B) Hepatomegaly occurs in several lysosomal storage diseases. In Niemann-Pick disease, an accumulation of sphingomyelin also causes progressive neurodegeneration and cherry-red macular spots. In Hunter and Hurler syndromes, accumulation of heparan and dermatan sulfate results in developmental delay, skeletal abnormalities, and cardiac disease. In contrast, the liver is not typically affected in Fabry disease.

(Choice C) Neurofibrosarcomas are malignant peripheral nerve sheath tumors that arise from neurofibromas, which are soft, pink or flesh-colored, benign nerve sheath tumors often found on the trunk of patients with neurofibromatosis.

(Choice D) Optic atrophy, developmental regression, and seizures occur in Krabbe disease, a disorder characterized by galactocerebrosidase deficiency.

Educational objective:
In Fabry disease, α-galactosidase A deficiency causes accumulation of the sphingolipid globotriaosylceramide. The earliest manifestations of Fabry disease are neuropathic pain and

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accumulation of sphingomyelin also causes progressive neurodegeneration and cherry-red macular spots. In Hunter and Hurler syndromes, accumulation of heparan and dermatan sulfate results in developmental delay, skeletal abnormalities, and cardiac disease. In contrast, the liver is not typically affected in Fabry disease.

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(Choice D) Optic atrophy, developmental regression, and seizures occur in Krabbe disease, a disorder characterized by galactocerebrosidase deficiency.

Educational objective:
In Fabry disease, α-galactosidase A deficiency causes accumulation of the sphingolipid globotriaosylceramide. The earliest manifestations of Fabry disease are neuropathic pain and angiokeratomas. Glomerular (eg, proteinuria, renal failure), cardiac (eg, left ventricular hypertrophy), and cerebrovascular (eg, transient ischemic attack, stroke) complications develop in adulthood.

References

- Renal complications of Fabry disease in children

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A 20-year-old woman with cystic fibrosis comes to the clinic for routine follow-up. She has no concerns since her last visit 3 months ago. Vital signs are normal. Examination shows a hyperexpanded chest with equal aeration bilaterally. Fasting glucose level is 90 mg/dL. Plasma glucose level 2 hours after oral glucose tolerance testing is 185 mg/dL (normal: <140). Which of the following is the primary mechanism responsible for this patient's abnormal test result?

A. Decreased insulin production due to disruption of pancreatic islet cells
B. Decreased insulin production due to pancreatic islet cell autoantibodies
C. Increased glucagon secretion due to chronic malnutrition
D. Increased insulin degradation due to hypermetabolic needs
E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine

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A. Decreased insulin production due to disruption of pancreatic islet cells (81%)
B. Decreased insulin production due to pancreatic islet cell autoantibodies (4%)
C. Increased glucagon secretion due to chronic malnutrition (5%)
D. Increased insulin degradation due to hypermetabolic needs (2%)
E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine (7%)

Correct

81%
Answered correctly

01 min, 18 secs
Time Spent

01/05/2021
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Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation (eg, ΔF508) in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this patient. As the disease progresses, there is fasting hyperglycemia and increasing hemoglobin A1c levels.

Because early diagnosis and treatment with insulin are associated with improved pulmonary status and overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the

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overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the pathogenesis of type 1 diabetes mellitus. Islet cell destruction in CFRD is not an autoimmune process.

(Choice C) Although glucagon increases in response to starvation, chronic malnutrition is likely to result in glucagon resistance. In addition, glucagon-producing alpha islet cells are damaged along with beta cells in patients with CF, resulting in decreased glucagon secretion.

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

Educational objective:
Cystic fibrosis (CF) causes the accumulation of thick, viscous secretions in ducts throughout the body. CF-related diabetes occurs after the progressive destruction of pancreatic islet cells leads to decreased insulin production.

References

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A 60-year-old man comes to the office for follow-up after a recent emergency department visit due to cough. The patient was diagnosed with acute bronchitis and the symptoms resolved with symptomatic treatment. A chest x-ray obtained during that visit revealed no lung abnormalities, but the bones appeared osteopenic. The patient reports no bone pain and has had no fractures. He has a history of prostate cancer treated with radiation therapy and is taking leuprolide. The patient has no other medical problems and has no known drug allergies. He drinks a glass of wine daily and does not use tobacco or illicit drugs. He eats a balanced diet and exercises regularly. Blood pressure is 120/80 mm Hg and pulse is 80/min. Physical examination shows no abnormalities. A dual-energy x-ray absorptiometry (DXA) scan shows low bone mineral density. Which of the following is the most likely underlying mechanism of the observed finding in this patient?

A. Decreased estrogen and testosterone levels
B. Decreased intestinal calcium absorption
C. Impaired 25-hydroxycholecalciferol activation
D. Increased parathyroid hormone levels
E. Paraneoplastic effects of the cancer cells

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A. Decreased estrogen and testosterone levels
B. Decreased intestinal calcium absorption
C. Impaired 25-hydroxycholecalciferol activation
D. Increased parathyroid hormone levels
E. Paraneoplastic effects of the cancer cells

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- A. Decreased estrogen and testosterone levels (69%)
- B. Decreased intestinal calcium absorption (6%)
- C. Impaired 25-hydroxycholecalciferol activation (6%)
- D. Increased parathyroid hormone levels (5%)
- E. Paraneoplastic effects of the cancer cells (11%)

Correct

69%

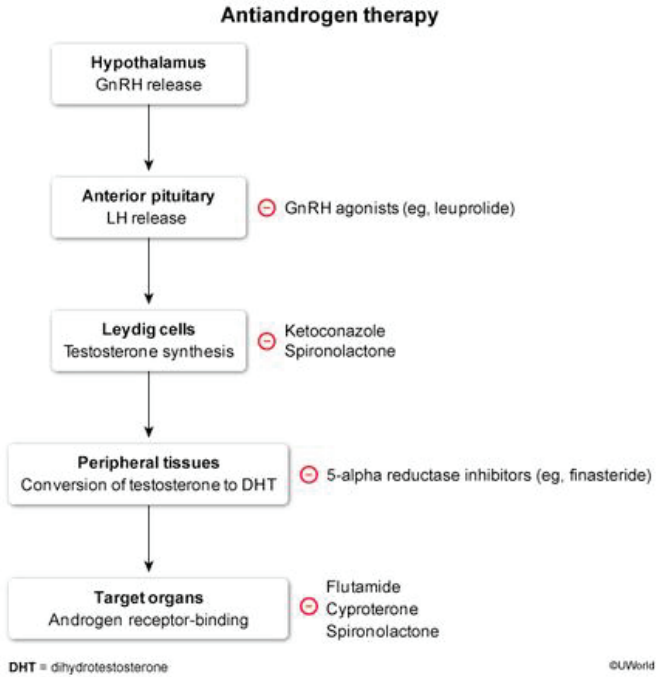
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Leuprolide is a **GnRH analog** used to suppress testosterone levels in the treatment of prostate cancer. When administered in a pulsatile fashion, leuprolide has agonist properties; however, long-term leuprolide use results in a continuous GnRH effect (also seen with GnRH infusion) that leads to the downregulation of GnRH receptors on gonadotropin cells in the pituitary gland. This suppresses pituitary LH release and leads to the reduced production of testosterone by Leydig cells. The lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy.

Hypogonadism can lead to accelerated bone loss and increased risk for **osteoporosis**. In male patients, androgens are aromatized to **estrogens**, which play a large role in bone homeostasis, largely by inhibiting osteoclast-driven cortical bone resorption. Androgens also act on osteoblasts and osteocytes in trabecular (sometimes called cancellous or spongy) bone to preserve bone density.

(Choice B) Glucocorticoids (eg, prednisone) and proton pump inhibitors (eg, omeprazole) are associated with an increased risk of osteoporosis, at least partly due to the decreased intestinal absorption of calcium. GnRH analogs have little effect on intestinal calcium absorption.

(Choices C and D) Elevated parathyroid hormone (PTH) levels stimulate osteoclast activity and release of calcium from bone, increasing the risk of osteoporosis. Similarly, low vitamin D concentrations lead to impaired calcium absorption with a compensatory increase in PTH. Conversion of 25-hydroxyvitamin D (ie,

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(Choices C and D) Elevated parathyroid hormone (PTH) levels stimulate osteoclast activity and release of calcium from bone, increasing the risk of osteoporosis. Similarly, low vitamin D concentrations lead to impaired calcium absorption with a compensatory increase in PTH. Conversion of 25-hydroxyvitamin D (ie, 25-hydroxycholecalciferol) to its active form, 1,25-dihydroxyvitamin D, by 1-alpha-hydroxylase (stimulated by PTH) occurs in the kidneys; this is one of the reasons that patients with chronic kidney disease are at increased risk of osteoporosis. However, this patient does not have a history of chronic kidney disease or hyperparathyroidism, and the vitamin D–PTH axis is not significantly influenced by leuprolide use.

(Choice E) Humoral hypercalcemia of malignancy (HHM) is a paraneoplastic syndrome due to release of PTH-related protein (PTHrP) by malignant cells. PTHrP is structurally similar to PTH and acts on the PTH-1 receptor. HHM is most commonly seen in squamous cell carcinoma (eg, lung), transitional cell carcinomas, and breast and ovarian cancers. It typically presents with severe, symptomatic hypercalcemia (eg, constipation, lethargy) rather than osteoporosis.

Educational objective:

Long-term use of GnRH agonists (eg, leuprolide) suppresses pituitary LH release and leads to the reduced production of testosterone. The lower levels of circulating testosterone produce a clinical effect similar to that of surgical orchiectomy and can lead to accelerated bone loss and increased risk for osteoporosis.

References

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A collection of tan fat-containing tissue is found around the kidneys and adrenal glands of a newborn during surgery. Surgical removal of the tissue would most likely contribute to:

A. Fasting hypoglycemia
B. Hypercholesterolemia
C. Fasting ketonemia
D. Lactic acidosis
E. Hypothermia

Submit

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A collection of tan fat-containing tissue is found around the kidneys and adrenal glands of a newborn during surgery. Surgical removal of the tissue would most likely contribute to:

- A. Fasting hypoglycemia (14%)
- B. Hypercholesterolemia (4%)
- C. Fasting ketonemia (3%)
- D. Lactic acidosis (3%)
- ✓ E. Hypothermia (74%)

Correct

74% Answered correctly

28 secs Time Spent

01/30/2021 Last Updated

Explanation

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Brown adipose tissue comprises 5% of body mass in neonates. It is also found in hibernating animals, but is present in very small amounts in adult humans. The main function of brown adipose tissue is heat production **(Choice E)**. Neonates have many physiological traits that make them more susceptible to hypothermia, such as an immature nervous system, a high body surface area to volume ratio and a decreased ability to shiver for heat production. Heat production by brown adipose tissue is, therefore, necessary for neonatal survival.

White adipose tissue is composed of cells that contain one intracytoplasmic fat droplet. Unlike white adipocytes, brown adipocytes possess several small intracytoplasmic fat vacuoles and considerably more mitochondria. The drastically increased number of mitochondria in these cells gives brown adipose tissue its tan color. Brown adipose tissue has a higher oxygen requirement and contains more capillaries than white adipose tissue.

In the majority of human cells, mitochondria are the sites of ATP production. In the mitochondria of brown adipose tissue electron transport and phosphorylation are uncoupled. The protons pumped out by electron transport chain return to the matrix via the mitochondrial membrane protein thermogenin, also known as an uncoupling protein. Thus no ATP is synthesized, and the energy released by electron transport is dissipated as heat.

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dissipated as heat.

(Choice A) A defect in gluconeogenesis or glycogenolysis would lead to fasting hypoglycemia. These processes primarily occur in the liver.

(Choice B) Hypercholesterolemia is most commonly due to a genetic / familial predisposition for high serum cholesterol levels. It may also be induced by diets high in cholesterol.

(Choice C) Ketonemia occurs when the liver is depleted of glycogen and utilizes body fat for gluconeogenesis. It occurs during sleep, fasting, starvation, and due to metabolic disturbances in diabetes mellitus.

(Choice D) Lactic acidosis results in states of tissue hypoxia or in the presence of defects in oxidative phosphorylation because pyruvate generated by glycolysis is converted to lactate rather than acetyl-CoA in these states.

Educational Objective:
Brown adipose tissue is found in newborns and in hibernating mammals. Brown adipose cells contain several intracytoplasmic fat droplets and many more mitochondria than white adipose cells. They function to produce heat by uncoupling oxidative phosphorylation with the protein thermogenin.

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A 40-year-old woman is evaluated for intermittent headaches, insomnia, diaphoresis, and unintentional weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

A. Adrenal cortex
B. Adrenal medulla
C. Ovary
D. Parathyroid gland
E. Thyroid follicles

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weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

A. Adrenal cortex (3%)
B. Adrenal medulla (85%)
C. Ovary (1%)
D. Parathyroid gland (1%)
E. Thyroid follicles (8%)

Correct
85%
01 min, 25 secs
11/20/2020

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Pheochromocytoma	
Pathogenesis	• Arises from neuroendocrine cells in **adrenal medulla** • 25% inherited: ◦ *VHL* gene (von Hippel-Lindau) ◦ *RET* gene (multiple endocrine neoplasia type 2) ◦ *NF1* gene (neurofibromatosis) • Symptoms result from **increased catecholamine secretion**
Symptoms	• Headache • Tachycardia/palpitations • Sweating • Hypertension
Rule of 10s	• 10% bilateral • 10% extraadrenal (paragangliomas) • 10% malignant
Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

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Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

Pheochromocytoma is a tumor of the **chromaffin cells** of the **adrenal medulla** characterized by excess production of **catecholamines** (norepinephrine, epinephrine, dopamine). Fluctuating catecholamine release results in increased vascular tone and hypertension, often associated with episodic headache, diaphoresis, and palpitations. The diagnosis is confirmed by detecting elevated levels of urinary and plasma catecholamines and metanephrines (catecholamine breakdown products).

Histopathology shows a highly vascular tumor with nests of spindle-shaped or polygonal cells. The neurohormonal character of the cells is confirmed with stains for **synaptophysin**, **chromogranin**, and **neuron-specific enolase**, and electron microscopy may show dense membrane-bound granules containing catecholamines.

(Choices A and C) Syndromes associated with steroid hormone-producing tumors of the adrenal cortex include hypercortisolism (Cushing syndrome), hyperaldosteronism (hypertension, hypokalemia, metabolic alkalosis), and hyperandrogenism (hirsutism, acne, androgenetic hair loss). Metabolically active ovarian tumors also can cause hyperandrogenism. Overproduction of steroid hormones is apparent on electron microscopy as well-developed smooth endoplasmic reticulum rather than membrane-bound secretory granules.

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tumors also can cause hyperandrogenism. Overproduction of steroid hormones is apparent on electron microscopy as well-developed smooth endoplasmic reticulum rather than membrane-bound secretory granules.

(Choice D) Parathyroid adenomas (or carcinomas) cause primary hyperparathyroidism resulting in hypercalcemia. Characteristic symptoms include constipation, abdominal pain, bone pain, and neuropsychiatric symptoms.

(Choice E) Toxic nodular thyroid disease could produce this patient's symptoms (eg, diaphoresis, weight loss). However, metabolically active thyroid adenomas typically show a follicular structure, with uniform cells and large amounts of follicular colloid.

Educational objective:

Pheochromocytoma is a tumor arising from the chromaffin cells of the adrenal medulla characterized by excess production of catecholamines. Clinical features include episodic hypertension, diaphoresis, and palpitations. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules, and immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase.

References

- Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline

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A 45-year-old previously healthy man comes to the office due to worsening muscle pain and weakness over the past 6 months. Carrying heavy items such as groceries has become increasingly difficult, and any prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

A. 24-hour urinary cortisol excretion
B. Acetylcholine receptor antibody titers
C. CT scan of the chest
D. Muscle biopsy
E. Serum TSH level

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prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

A. 24-hour urinary cortisol excretion (12%)
B. Acetylcholine receptor antibody titers (10%)
C. CT scan of the chest (5%)
D. Muscle biopsy (24%)
✓ E. Serum TSH level (46%)

Correct
46%
01 min, 14 secs
09/28/2020

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Common causes of myopathy		
Disorder	**Clinical features**	**Creatine kinase**
Glucocorticoid-induced myopathy	• Progressive proximal muscle weakness & atrophy **without pain** • Lower extremity muscles more involved	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in shoulder, neck & pelvic girdle • Worse in morning & with activity	Normal
Inflammatory myopathies (eg, polymyositis, dermatomyositis)	• Proximal muscle weakness • **Skin rash** & **inflammatory arthritis** possibly present	↑
Statin-induced	• Proximal muscle pain & weakness usually within weeks to months **after starting**	↑

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Polymyalgia rheumatica	• Muscle **pain & stiffness** in shoulder, neck & pelvic girdle • Worse in morning & with activity	Normal
Inflammatory myopathies (eg, polymyositis, dermatomyositis)	• Proximal muscle weakness • **Skin rash** & **inflammatory arthritis** possibly present	↑
Statin-induced myopathy	• Proximal muscle pain & weakness usually within weeks to months **after starting statin**	↑
Hypothyroid myopathy	• Muscle pain, cramps & weakness involving the proximal muscles • **Delayed tendon reflexes** & myoedema • Features of hypothyroidism	↑

An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include

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An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include hypothyroidism, muscular dystrophies, inflammatory muscle diseases, and medications such as HMG-CoA reductase inhibitors.

This patient's fatigue, **weight gain**, **bradycardia**, and **brittle nails** are highly suggestive of **hypothyroid myopathy**. Decreased thyroid hormone levels impair muscle glycogen and triglyceride use and increase oxidative stress, resulting in myocyte injury. Patients typically presents with myalgias, proximal muscle weakness, decreased exercise tolerance, and cramping. **Myoedema** (focal muscle contraction at the site of percussion) and **delayed relaxation** of deep tendon reflexes are characteristic findings that are caused by impaired reuptake of calcium by the sarcoplasmic reticulum.

Hypothyroid myopathy and elevations in CK can be the first signs of hypothyroidism and can precede other manifestations by months to years. The diagnosis can be confirmed with an **elevated TSH level**.

(Choice A) A 24-hour urine cortisol test is used as an initial test for Cushing syndrome. This disorder can present with proximal muscle weakness and atrophy due to the direct catabolic effects of cortisol on skeletal muscle. However, there is no associated muscle pain or rise in CK, reflexes are normal, and other cushingoid features (eg, striae, dorsocervical fatty hypertrophy) are usually present.

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receptors on the postsynaptic membrane of the neuromuscular junction. It presents with fluctuating weakness that worsens through the day. Lambert-Eaton syndrome is a paraneoplastic disorder associated with small cell carcinoma of the lung (which can be identified on CT scan). It is caused by autoantibodies against voltage-gated calcium channels on the presynaptic membrane, which cause decreased release of acetylcholine. These disorders affect the neuromuscular junction rather than the muscle itself, and CK is normal.

(Choice D) Muscle biopsy is often needed for diagnosis of inflammatory myositis (eg, polymyositis, dermatomyositis). However, this patient has symptoms suggestive of hypothyroidism (eg, weight gain, bradycardia, brittle nails), and histologic findings in hypothyroid myopathy are often nonspecific.

Educational objective:
Hypothyroid myopathy presents with myalgias, proximal muscle weakness, elevated creatine kinase levels, and delayed relaxation of deep tendon reflexes. The diagnosis can be confirmed with an elevated TSH level. Other common causes of myopathy with elevated creatine kinase levels include inflammatory myopathies, muscular dystrophies, and HMG-CoA reductase inhibitors.

Pathophysiology | Endocrine, Diabetes & Metabolism | Hypothyroidism

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A 60-year-old man comes to the office for follow-up of type 2 diabetes mellitus. His current treatment regimen includes metformin and a once-daily injection of a long-acting subcutaneous insulin. The patient is adherent with the treatment and has a healthy lifestyle. Review of his home glucose measurements shows that his postprandial glucose levels are frequently elevated; however, fasting levels are normal. He has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory testing reveals hemoglobin A1c is 8.3%. Additional insulin therapy 3 times a day before each meal is planned to improve glycemic control. Which of the following types of insulin would be most appropriate for the additional therapy?

A. Insulin aspart
B. Insulin degludec
C. Insulin detemir
D. Insulin glargine
E. NPH insulin

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regimen includes metformin and a once-daily injection of a long-acting subcutaneous insulin. The patient is adherent with the treatment and has a healthy lifestyle. Review of his home glucose measurements shows that his postprandial glucose levels are frequently elevated; however, fasting levels are normal. He has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Physical examination shows no abnormalities. Laboratory testing reveals hemoglobin A1c is 8.3%. Additional insulin therapy 3 times a day before each meal is planned to improve glycemic control. Which of the following types of insulin would be most appropriate for the additional therapy?

- A. Insulin aspart (77%)
- B. Insulin degludec (1%)
- C. Insulin detemir (3%)
- D. Insulin glargine (9%)
- E. NPH insulin (8%)

Correct

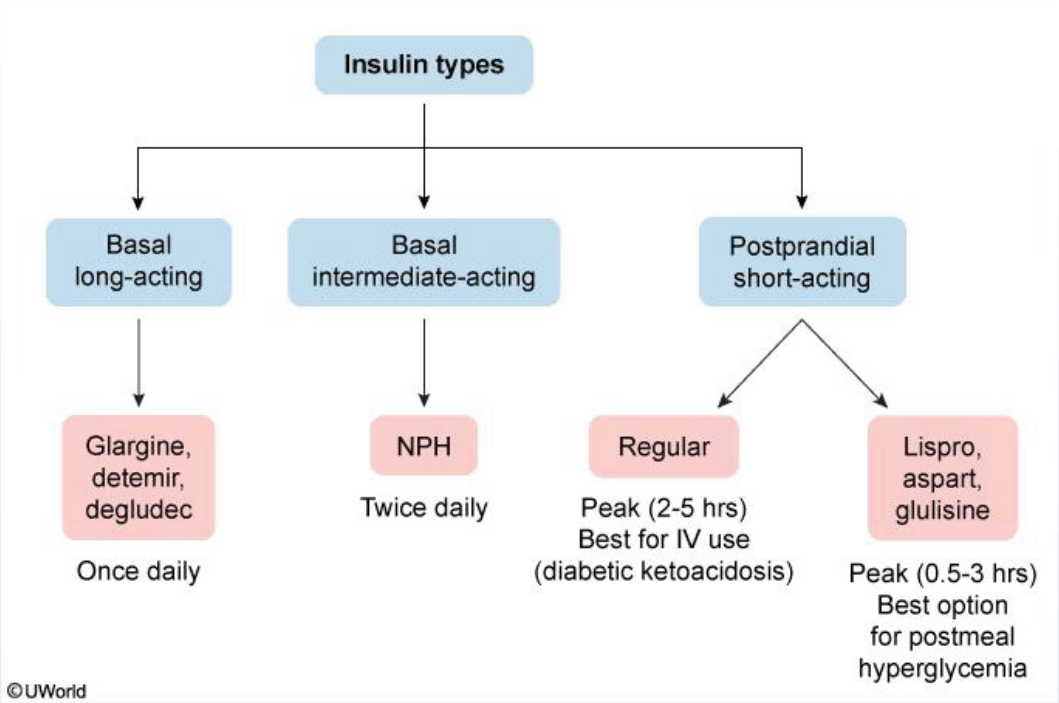
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The beta cells of the pancreas produce insulin continuously at a low level. After meals, insulin secretion increases briefly to control the postprandial rise in blood glucose. Commercial insulin analogs are

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The beta cells of the pancreas produce insulin continuously at a low level. After meals, insulin secretion increases briefly to control the postprandial rise in blood glucose. Commercial insulin analogs are formulated with different pharmacokinetic properties that can be used to replicate physiologic insulin secretion:

- Long-acting insulins have an extended duration of action and little or no peak in activity. They are typically given once daily to mimic basal insulin secretion.
- Rapid-acting insulins are quickly taken up from the injection site and then rapidly cleared. They are given at mealtimes to replicate the normal postprandial increase in insulin secretion.

This patient has normal fasting glucose levels, suggesting that his long-acting basal insulin therapy is appropriate. However, his postprandial glucose readings are elevated. Adding a **rapid-acting insulin analog** (eg, **aspart**, lispro, glulisine) with meals would **reduce postprandial glucose** and improve overall glycemic control. Because the rapid-acting insulins are cleared quickly, they have minimal residual effect on fasting glucose levels. Regular insulin also can be given at mealtimes but forms dimers and hexamers, which cause a slight delay in uptake from the injection site and prolongation of effect.

(Choices B, C, and D) Insulin degludec has addition of a hexadecanedioic acid residue, which causes

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which cause a slight delay in uptake from the injection site and prolongation of effect.

(Choices B, C, and D) Insulin degludec has addition of a hexadecanedioic acid residue, which causes polymer formation at the injection site and slowed uptake. Detemir has a fatty acid side chain added to lysine B29 of the insulin molecule, which causes it to bind circulating albumin and slowly dissociate. Glargine has a pH of 4 and forms a microprecipitate at the injection site, resulting in delayed absorption. These analogs all have a long duration of action with minimal peak and are used for basal insulin therapy. As such, they would be poor choices for controlling postprandial glucose.

(Choice E) NPH is a crystalline suspension of insulin with protamine and zinc, which delays absorption from the injection site. NPH is an intermediate-acting insulin that is typically given twice daily; although it has a noticeable peak effect, it is used primarily as basal insulin.

Educational objective:

Long-acting insulin analogs (eg, degludec, detemir, glargine) have an extended duration of action without a noticeable peak in activity and are typically given once daily to mimic basal insulin secretion. Rapid-acting insulins (eg, aspart, lispro, glulisine) are quickly absorbed from the injection site and are given at mealtimes to replicate postprandial insulin secretion.

References

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A 24-year-old man diagnosed with diabetes mellitus 2 years ago is brought to the emergency department after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

A. Adipose tissue
B. Adrenals
C. Kidney
D. Liver
E. Pancreas
F. Skeletal muscles
G. Small intestine

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after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

- A. Adipose tissue (2%)
- B. Adrenals (1%)
- C. Kidney (0%)
- ✓ D. Liver (86%)
- E. Pancreas (3%)
- F. Skeletal muscles (4%)
- G. Small intestine (0%)

Correct

86%

36 secs

09/19/2020

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Glucagon increases serum glucose by increasing hepatic glucose production via **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (production of glucose from noncarbohydrate sources). Glucagon-induced glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

Glucagon functions by stimulating G protein–coupled receptors on hepatocytes, increasing intracellular cAMP concentration and activating protein kinase A. This leads to activation of the key glycogenolytic enzyme, glycogen phosphorylase. It also stimulates gluconeogenesis by activating rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose-2,6-bisphosphate levels (inhibiting glycolysis).

(Choices A, B, and F) Epinephrine from the adrenals increases glucose by multiple mechanisms, including increased glycogenolysis and gluconeogenesis in the liver and decreased glucose uptake by skeletal muscle. Epinephrine also causes increased alanine release from skeletal muscle, which serves as a source of gluconeogenesis in the liver. In adipose tissue, epinephrine increases the breakdown of triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's

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triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's glucose. When hypoglycemia is sustained, gluconeogenesis in the renal cortex becomes an important glucose source. Epinephrine is more effective than glucagon in stimulating renal gluconeogenesis.

(Choice E) Glucagon and insulin are pancreatic hormones that act as key blood glucose regulators. Insulin decreases blood glucose levels and suppresses glucagon secretion. Although it sounds counterintuitive, glucagon stimulates insulin secretion by acting on the pancreatic beta cells (allowing glucose to be taken up by insulin-sensitive tissues).

(Choice G) The treatment of choice in hypoglycemic patients without an altered sensorium is to administer glucose orally as glucose is a monosaccharide that gets absorbed rapidly from the gastrointestinal tract.

Educational objective:
Glucagon increases serum glucose by increasing hepatic glycogenolysis and gluconeogenesis. Glucagon also stimulates insulin secretion from the pancreas. Unlike epinephrine, glucagon has an insignificant effect on glucose homeostasis in the skeletal muscle, adipose tissue, and renal cortex.

References

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A 34-year-old woman comes to the office with a 2-week history of palpitations, excessive sweating, and anxiety. The patient has obesity and has been unsuccessful in achieving significant weight loss with diet and exercise. In an attempt to lose weight, she has been taking excessive amounts of levothyroxine given to her by a friend. Pulse is 110/min. Physical examination shows sweaty palms and a soft, nontender, normal-sized thyroid gland. Laboratory evaluation reveals suppressed TSH and elevated free thyroxine (T4). Which of the following additional findings is most likely to be present in this patient?

	Radioactive iodine uptake	Serum thyroglobulin level	Total triiodothyronine (T3)
A.	↑	↑	↑
B.	↓	↑	↑
C.	↓	↓	↑
D.	↓	↓	Normal
E.	Normal	Normal	↑

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anxiety. The patient has obesity and has been unsuccessful in achieving significant weight loss with diet and exercise. In an attempt to lose weight, she has been taking excessive amounts of levothyroxine given to her by a friend. Pulse is 110/min. Physical examination shows sweaty palms and a soft, nontender, normal-sized thyroid gland. Laboratory evaluation reveals suppressed TSH and elevated free thyroxine (T4). Which of the following additional findings is most likely to be present in this patient?

	Radioactive iodine uptake	Serum thyroglobulin level	Total triiodothyronine (T3)	
A.	↕	↕	↕	(9%)
B.	↓	↑	↑	(17%)
C. ✓	↓	↓	↑	(44%)
D.	↓	↓	Normal	(10%)
E.	~~Normal~~	~~Normal~~	↕	(18%)

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Explanation

Differential diagnosis of thyrotoxicosis			
	Serum TSH	**Serum thyroglobulin**	**Radioiodine uptake**
Increased thyroid hormone production (eg, Graves disease)	↓	↑	↑
Destruction of thyroid follicles (eg, subacute thyroiditis)	↓	↑↑	↓
Exogenous thyroid hormone	↓	↓	↓
Central hyperthyroidism (eg, pituitary adenoma)	↑	↑	↑

This patient has **exogenous thyrotoxicosis**, which can occur intentionally due to abuse of thyroid preparations (eg, **levothyroxine**, porcine thyroid extracts) or inadvertently due to errors in treatment of hypothyroidism. Symptoms resemble endogenous hyperthyroidism and include weight loss, tremor, heat

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This patient has **exogenous thyrotoxicosis**, which can occur intentionally due to abuse of thyroid preparations (eg, **levothyroxine**, porcine thyroid extracts) or inadvertently due to errors in treatment of hypothyroidism. Symptoms resemble endogenous hyperthyroidism and include weight loss, tremor, heat intolerance, and tachycardia/palpitations.

In addition to elevated serum thyroxine (T4) and suppressed TSH, laboratory testing in exogenous thyrotoxicosis typically shows the following:

- **Radioactive iodine uptake** (RAIU): A radioiodine tracer is administered followed by scintigraphy of the thyroid gland; RAIU correlates with the organification of iodine and the synthesis of new thyroid hormone. In exogenous thyrotoxicosis, endogenous thyroid hormone synthesis is suppressed, so **RAIU is low**. If thyroid ultrasound is performed, Doppler shows decreased blood flow.
- **Thyroglobulin**: Thyroglobulin is a large glycoprotein in thyroid follicles that serves as a source of tyrosine residues for thyroid hormone synthesis. Small amounts of thyroglobulin are normally released with thyroid hormone, although greater quantities may be released in states of increased thyroid hormone synthesis or follicular destruction. In exogenous thyrotoxicosis, thyroid metabolic activity is low, and **serum thyroglobulin is also low**.
- **Triiodothyronine (T3)**: T3 is derived primarily from T4 by deiodination in peripheral tissues, although

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low, and **serum thyroglobulin is also low**.

- **Triiodothyronine (T3)**: T3 is derived primarily from T4 by deiodination in peripheral tissues, although small amounts are coreleased from the thyroid with T4. Exogenous levothyroxine is readily converted to T3, so T3 levels are also usually **elevated**.

(Choice A) Elevated RAIU, thyroglobulin, and T3 suggest increased metabolic activity in the thyroid (eg, Graves disease).

(Choice B) Elevated thyroglobulin and T3 with a suppressed RAIU suggest the destruction of thyroid follicles and the release of preformed thyroid hormone (eg, subacute thyroiditis).

(Choice D) Following thyroidectomy, patients with thyroid cancer are often treated with levothyroxine to achieve a subclinical hyperthyroid state; the suppressed TSH level avoids stimulation of residual malignant thyroid cells. RAIU and thyroglobulin are low because the thyroid is absent, but because the target hyperthyroid state is mild/subclinical, T3 is often normal or only slightly elevated.

(Choice E) Thyroid hormone is carried in the circulation bound to plasma proteins, especially thyroid-binding globulin (TBG). TBG is elevated in hyperestrogenic states (eg, pregnancy, estrogen-based contraceptives); thyroid hormone production increases transiently to fill the increased number of binding

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follicles and the release of preformed thyroid hormone (eg, subacute thyroiditis).

(Choice D) Following thyroidectomy, patients with thyroid cancer are often treated with levothyroxine to achieve a subclinical hyperthyroid state; the suppressed TSH level avoids stimulation of residual malignant thyroid cells. RAIU and thyroglobulin are low because the thyroid is absent, but because the target hyperthyroid state is mild/subclinical, T3 is often normal or only slightly elevated.

(Choice E) Thyroid hormone is carried in the circulation bound to plasma proteins, especially thyroid-binding globulin (TBG). TBG is elevated in hyperestrogenic states (eg, pregnancy, estrogen-based contraceptives); thyroid hormone production increases transiently to fill the increased number of binding sites, then activity (eg, RAIU, serum thyroglobulin) returns to normal. Total T3 and T4 are elevated, but free hormone levels are normal.

Educational objective:
In exogenous thyrotoxicosis, radioactive iodine uptake and serum thyroglobulin level are low, indicating suppression of endogenous thyroid metabolic activity. Serum T3 levels are often elevated.

Physiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

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An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

A. Acetyl CoA carboxylase
B. Acyl CoA synthetase
C. ATP citrate lyase
D. Glucose-6-phosphate dehydrogenase
E. Glycerol kinase

Submit

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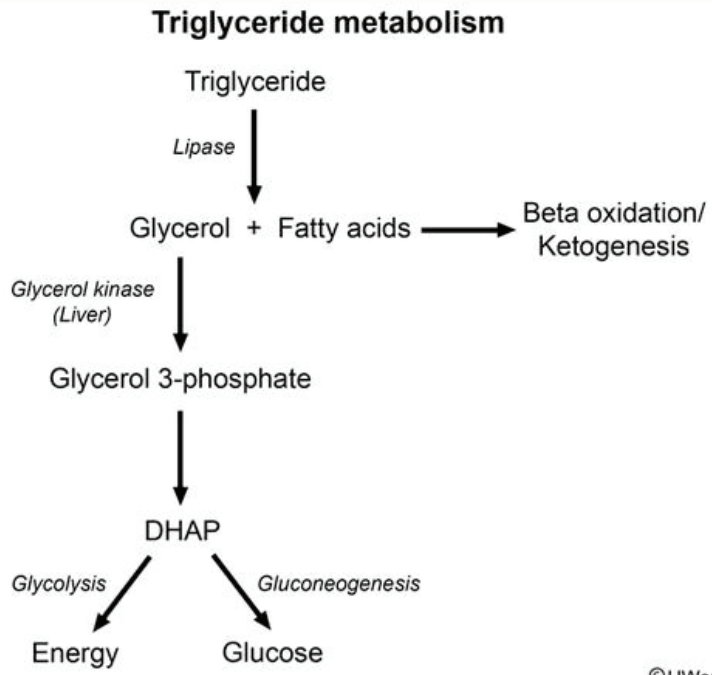
- ✗ A. Acetyl CoA carboxylase (41%)
- B. Acyl CoA synthetase (25%)
- C. ~~ATP citrate lyase~~ (4%)
- D. ~~Glucose-6-phosphate dehydrogenase~~ (8%)
- ✓ E. Glycerol kinase (19%)

Incorrect

19% 01 min, 24 secs 11/02/2020

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Energy Glucose

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This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency. Triglycerides stored in adipose tissue are metabolized to free fatty acids and **glycerol** by hormone-sensitive lipase in response to low insulin and high catecholamine levels. Adipocytes are unable to metabolize glycerol, so it is secreted into the circulation and transported to the liver, where it is phosphorylated to glycerol-3-phosphate by **glycerol kinase**. Glycerol-3-phosphate is subsequently converted by glycerol-3-phosphate dehydrogenase to dihydroxyacetone phosphate (DHAP), which can be used to produce **glucose** through **gluconeogenesis**.

(Choice A) Acetyl CoA carboxylase is a biotin-dependent enzyme present in both liver and adipose tissues. It catalyzes the first committed step in fatty acid synthesis, the conversion of acetyl CoA to malonyl CoA.

(Choice B) Fatty acids must first be activated by acyl CoA synthetase in the cytoplasm in order to undergo beta-oxidation in mitochondria. Although beta-oxidation of fatty acids is increased in diabetic ketoacidosis, the resulting acetyl-CoA is used for energy and ketone body formation (not glucose production).

(Choice C) In contrast to fatty acid oxidation, which occurs in mitochondria, fatty acid synthesis occurs in the cytosol. Acetyl CoA generated in mitochondria during glycolysis is transferred to the cytosol as citrate

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(Choice B) Fatty acids must first be activated by acyl CoA synthetase in the cytoplasm in order to undergo beta-oxidation in mitochondria. Although beta-oxidation of fatty acids is increased in diabetic ketoacidosis, the resulting acetyl-CoA is used for energy and ketone body formation (not glucose production).

(Choice C) In contrast to fatty acid oxidation, which occurs in mitochondria, fatty acid synthesis occurs in the cytosol. Acetyl CoA generated in mitochondria during glycolysis is transferred to the cytosol as citrate. In the cytoplasm, ATP citrate lyase converts citrate back into acetyl CoA that can be used for fatty acid chain elongation.

(Choice D) Glucose-6-phosphate dehydrogenase is the first enzyme of the hexose monophosphate (HMP) shunt. The HMP shunt produces pentose sugars for nucleotide synthesis and NADPH, which is necessary for cholesterol and fatty acid biosynthesis.

Educational objective:
Glycerol produced by the degradation of triglycerides in adipose tissue can be used by glycerol kinase in the liver and kidney to synthesize glucose during gluconeogenesis.

Biochemistry	Endocrine, Diabetes & Metabolism	Triglyceride metabolism
Subject	System	Topic

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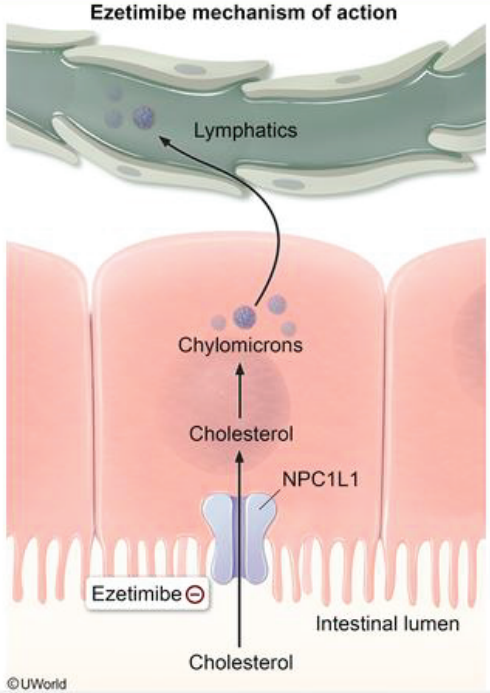
A 68-year-old man reports myalgia and fatigue during a follow-up office visit. The patient has been taking high-intensity statin therapy since he had an acute myocardial infarction several weeks ago. His other medical problems include hypertension and type 2 diabetes mellitus. On examination, there is mild generalized muscle tenderness. Serum creatine kinase level is 456 U/L. Vitamin D and TSH levels are within normal range. The patient's statin therapy is discontinued, and he is started on a medication that inhibits cholesterol absorption at the brush border of the small intestine. Which of the following drugs was most likely started in this patient?

A. Colesevelam (9%)
B. Ezetimibe (77%)
C. Fenofibrate (10%)
D. Nicotinic acid (1%)
E. PCSK9 inhibitor (2%)

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Cholesterol-lowering agents commonly work in 1 of 3 ways:

- Decreasing hepatic cholesterol synthesis
- Decreasing intestinal cholesterol absorption
- Altering cholesterol transport between the blood and tissues

Ezetimibe decreases **intestinal absorption** of cholesterol by inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter protein, which transports dietary cholesterol from the gastrointestinal lumen into intestinal enterocytes. As a result, the total amount of dietary cholesterol reaching the liver decreases, lowering intrahepatocyte cholesterol levels. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

(Choice A) Bile acid sequestrants (eg, colesevelam) bind bile salts in the intestine, decreasing their reabsorption. Subsequent depletion of the bile acid pool causes upregulation of cholesterol 7-α-hydroxylase, which converts cholesterol into bile acids.

(Choice C) Fibrates activate peroxisome proliferator-activated receptor-alpha transcription factors, which leads to stimulation of lipoprotein lipase activity and a decrease in triglyceride levels.

(Choice D) Nicotinic acid inhibits hepatic triglyceride synthesis, which in turn reduces the liver's availability

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hydroxylase, which converts cholesterol into bile acids.

(Choice C) Fibrates activate peroxisome proliferator-activated receptor-alpha transcription factors, which leads to stimulation of lipoprotein lipase activity and a decrease in triglyceride levels.

(Choice D) Nicotinic acid inhibits hepatic triglyceride synthesis, which in turn reduces the liver's availability to synthesize VLDL particles that are subsequently metabolized into LDL in the circulation.

(Choice E) Proprotein convertase subtilisin kexin 9 (PCSK9) increases degradation of hepatic LDL receptors. Alirocumab is a monoclonal antibody against PCSK9 that blocks this effect, resulting in increased availability of LDL receptors on hepatocyte membranes and subsequently increased clearance of LDL from the blood.

Educational objective:

Ezetimibe reduces intestinal absorption of cholesterol. As a result, the amount of dietary cholesterol reaching the liver decreases. To compensate, the liver increases LDL receptor expression, which draws cholesterol out of the circulation.

References

- Ezetimibe--a new approach in hypercholesterolemia management.
- Inactivating mutations in NPC1L1 and protection from coronary heart disease

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Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Side effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ **LDL** • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty	• ↓ VLDL synthesis	• ↓ Triglycerides	

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Cholesterol-lowerin

- Decreasing he
- Decreasing int
- Altering choles

Ezetimibe decreas
(NPC1L1) transpor
intestinal enterocyt
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which draws choles

(Choice A) Bile ac
reabsorption. Subs
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Cholesterol-lowerin

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Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

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Cholesterol-lowerin

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- Altering choles

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Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

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A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10 lb) in the last 3 weeks. The patient has no past medical problems. His father has type 1 diabetes mellitus. Physical examination shows dry mucous membranes. Laboratory studies reveal blood glucose of 455 mg/dL, normal anion gap, and hemoglobin A1c of 11.3%. The patient is diagnosed with type 1 diabetes, and treatment with insulin is initiated. In addition to lowering blood glucose, insulin increases glycogen synthesis in hepatocytes. Activation of which of the following molecules most likely promotes this metabolic effect?

A. Janus kinase (JAK)
B. Lipoxygenase
C. Phospholipase C
D. Protein kinase A
E. Protein phosphatase

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- A. Janus kinase (JAK) (23%)
- B. Lipoxygenase (1%)
- C. Phospholipase C (9%)
- D. Protein kinase A (27%)
- E. Protein phosphatase (38%)

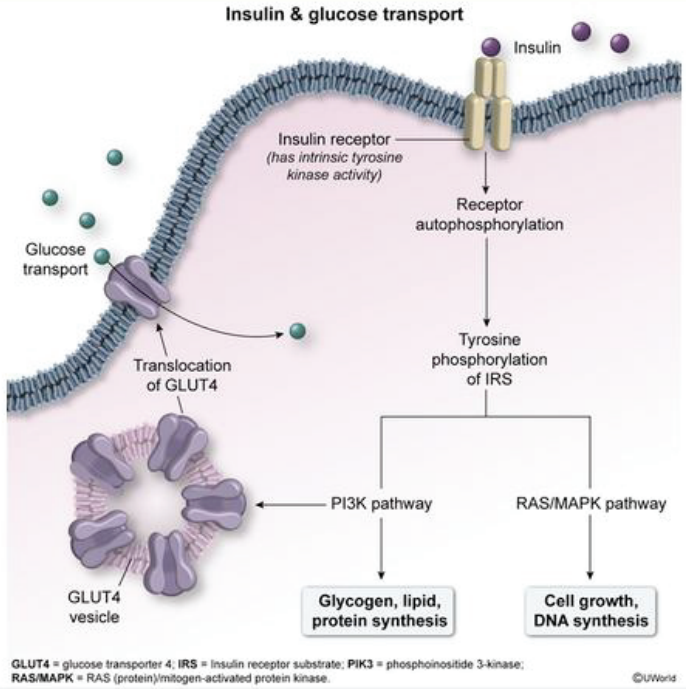
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GLUT4 = glucose transporter 4; **IRS** = Insulin receptor substrate; **PIK3** = phosphoinositide 3-kinase; **RAS/MAPK** = RAS (protein)/mitogen-activated protein kinase.

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Insulin decreases blood glucose levels by increasing glucose uptake into skeletal muscle and adipocytes. In addition to having glucose lowering effects, insulin is an anabolic hormone that promotes synthesis of glycogen, triglycerides, nucleic acids, and proteins. Furthermore, insulin inhibits glycogenolysis and gluconeogenesis.

The surface receptor for insulin is a transmembrane protein with **intrinsic tyrosine kinase** activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that dephosphorylates glycogen synthase, leading to its activation.

(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor

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dephosphorylates glycogen synthase, leading to its activation.

(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor tyrosine kinase).

(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:

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(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:

Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates) glycogen synthase.

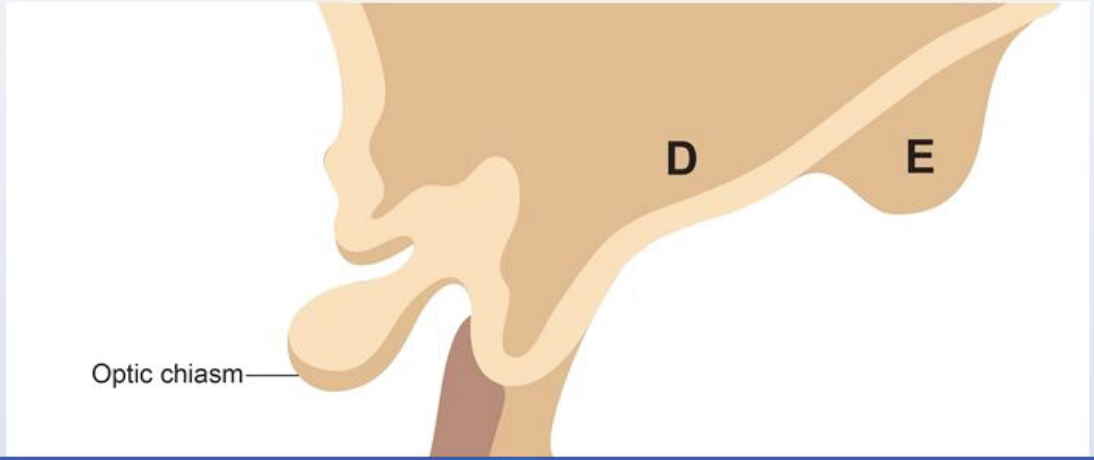
References

- Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions.

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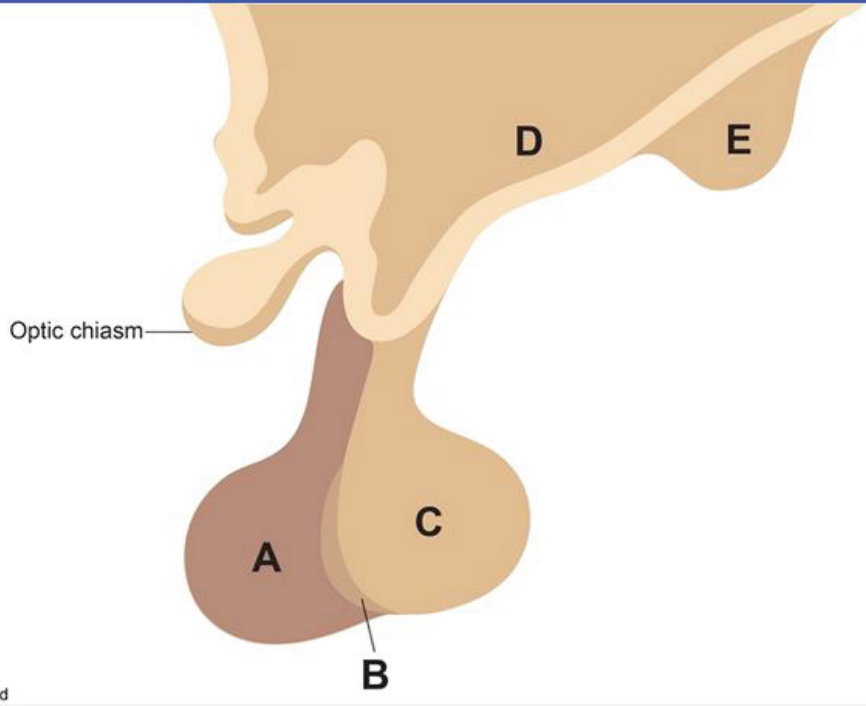
A 34-year-old woman comes to the clinic due to dizziness and mild confusion over the last week. The patient has a history of seizures beginning in childhood and was recently started on carbamazepine by her neurologist. Her temperature is 36.7 C (98 F), blood pressure is 121/72 mm Hg, pulse is 68/min, and respirations are 13/min. Physical examination is within normal limits. Laboratory studies show a low serum sodium concentration. It is determined that the patient's condition is caused by increased release of a hormone that is co-secreted with neurophysins. This hormone is most likely secreted into the circulation at which of the following sites?



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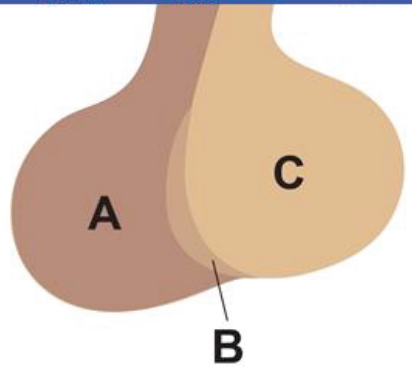
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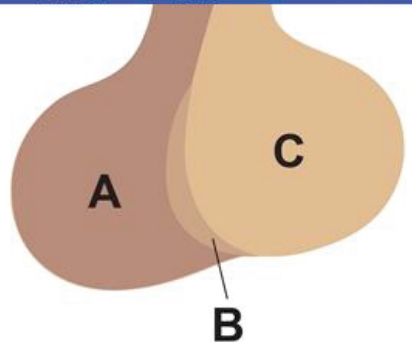
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- A.A (8%)
- B.B (4%)
- ✓ C.C (78%)
- D.D (7%)
- E.E (1%)

Correct

78%

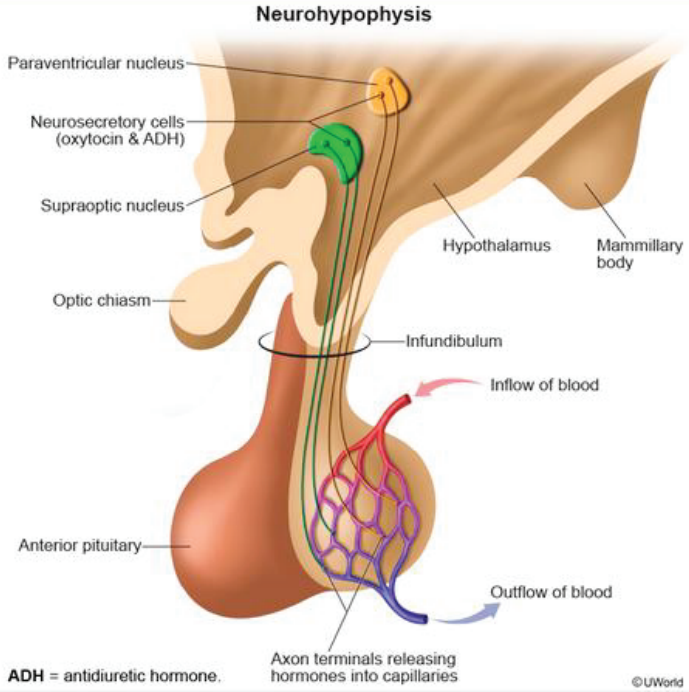
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This patient most likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**), which can be caused by a multitude of drugs, including **carbamazepine**, cyclophosphamide, and selective serotonin reuptake inhibitors.

Antidiuretic hormone (vasopressin) and oxytocin are **synthesized** within magnocellular neurons found in the supraoptic and paraventricular nuclei of the hypothalamus. Most magnocellular neurons produce either vasopressin or oxytocin. Once translated, these hormones are packaged into vesicles and travel via anterograde axonal transport to the posterior pituitary (neurohypophysis). There, the hypothalamic axons terminate into Herring bodies, which are specialized nerve terminals that act as storage sites for the secretory vesicles. These vesicles also contain proteins known as **neurophysins** that are involved in posttranslational hormone processing and stabilization during axonal transport. Vasopressin and oxytocin and their associated neurophysins are then **secreted** from the **posterior pituitary** into the hypophysial vein to enter the systemic circulation.

(Choice A) The anterior pituitary (adenohypophysis) is the glandular portion of the pituitary that lies closest to the optic chiasm. It is composed of various hormone-secreting cells, including somatotropes (growth hormone), lactotropes (prolactin), gonadotropes (FSH and LH), thyrotropes (TSH), and corticotropes (ACTH).

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(Choice B) This is the vestigial intermediate lobe of the pituitary gland, which is derived from the posterior wall of Rathke's pouch during embryonic development. It is not a significant source of secretory products in humans, but can secrete a small amount of melanocyte-stimulating hormone.

(Choices D and E) The posterior hypothalamus is involved in the control of sympathetic responses, including temperature regulation; the mammillary bodies are important for memory recall. These regions do not directly secrete hormones.

Educational objective:
Vasopressin and oxytocin are synthesized within neurons found in the paraventricular and supraoptic nuclei and are released into the circulation from axon terminals in the posterior pituitary. Neurophysins are involved in the posttranslational processing and stabilization of oxytocin and vasopressin within neurosecretory vesicles during transport to the posterior pituitary.

References

- Progressive decline of vasopressin secretion in familial autosomal dominant neurohypophyseal diabetes insipidus presenting a novel mutation in the vasopressin-neurophysin II gene.

Pathophysiology Endocrine, Diabetes & Metabolism SIADH

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A 58-year-old man is hospitalized due to sudden onset of chest pain. Blood pressure is 160/110 mm Hg and pulse is 90/min. BMI is 26.9 kg/m^2. A baseline ECG shows nonspecific ST-segment and T-wave abnormalities, and serial troponin measurements are normal. The patient's fasting plasma glucose level is 160 mg/dL, although he has not been diagnosed previously with diabetes mellitus. Serum triglyceride level is elevated, and the HDL level is low. Which of the following additional findings would be most suggestive of increased insulin resistance in this patient?

A. Decreased hepatic glucose production
B. Elevated LDL level
C. High urine ketone concentration
D. Increased glycogen stores in skeletal muscles
E. Increased waist circumference

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A. Decreased hepatic glucose production (4%)
B. Elevated LDL level (12%)
C. High urine ketone concentration (17%)
D. Increased glycogen stores in skeletal muscles (2%)
E. Increased waist circumference (62%)

Correct

62%
Answered correctly

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This patient has hypertension and likely **type 2 diabetes mellitus**. The primary defects in the pathophysiology of type 2 diabetes include **defective insulin secretion** from pancreatic beta cells and **insulin resistance** in peripheral tissues. Insulin resistance is caused by a number of genetic (eg, insulin receptor and postreceptor mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese (BMI 30-34.9 kg/m^2). A waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women is associated with a higher risk of insulin resistance.

The association of insulin resistance, increased visceral adiposity (ie, increased waist circumference), hypertension, and serum lipid abnormalities (high triglyceride levels, low HDL levels) is known as **metabolic syndrome** (sometimes called syndrome X). Patients with metabolic syndrome have increased rates of **cardiovascular events** and warrant careful risk factor management.

(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased

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(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased hepatic glucose production.

(Choice B) High LDL levels are an independent risk factor for atherosclerotic heart disease in patients with diabetes, but are not directly associated with increased insulin resistance. In contrast, insulin resistance is associated with high triglyceride and low HDL levels.

(Choice C) High urinary excretion of ketones suggests absolute insulin deficiency, as seen in type 1 diabetes, rather than insulin resistance. Patients with type 2 diabetes and insulin resistance typically have high circulating insulin levels that are more than adequate to suppress ketone formation.

(Choice D) Skeletal muscle is a major repository for ingested glucose due to insulin-mediated glucose uptake. In patients with insulin resistance, decreased glucose uptake in skeletal muscle leads to reduced glycogen synthesis and higher blood glucose levels.

Educational objective:
Visceral obesity as measured by waist circumference or waist-to-hip ratio is an important predictor of insulin resistance.

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A newborn boy is found to have markedly elevated serum TSH and low thyroxine on routine screening. Laboratory findings using a venous blood sample confirm the diagnosis. The patient was born at 39 weeks gestation to a 34-year-old healthy woman, who had been taking prenatal vitamins regularly. He has no symptoms or abnormal findings on clinical examination. Imaging studies reveal an ectopic thyroid gland just below the tongue. Which of the following is the most likely cause of this patient's otherwise normal physical examination despite abnormal thyroid laboratory findings?

A. Excess thyroxine production by an ectopic thyroid
B. Increased thyroid-binding globulin in pregnancy
C. Transplacental transfer of thyroid-stimulating antibody
D. Transplacental transfer of thyroxine
E. Transplacental transfer of TSH

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A. Excess thyroxine production by an ectopic thyroid (12%)
B. Increased thyroid-binding globulin in pregnancy (19%)
C. Transplacental transfer of thyroid-stimulating antibody (6%)
D. Transplacental transfer of thyroxine (53%)
E. Transplacental transfer of TSH (7%)

Correct

53%
Answered correctly

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Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*

*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

This infant has **primary hypothyroidism**, a congenital disorder that is most commonly caused by abnormal thyroid gland development (ie, agenesis, hypoplasia) or location (ectopy). During normal

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This infant has **primary hypothyroidism**, a congenital disorder that is most commonly caused by abnormal thyroid gland development (ie, agenesis, hypoplasia) or location (ectopy). During normal embryogenesis, the thyroid descends from the developing pharynx to its normal location anterior to the trachea. Abnormal migration results in an **ectopic thyroid** (eg, lingual, mediastinal), as seen in this patient.

Most patients with thyroid dysgenesis have hypothyroidism, with routine newborn screening findings of increased TSH and decreased thyroxine (T4) levels. However, **newborns** are typically **asymptomatic** for the first weeks due to the presence of **maternal T4**, which **crosses the placenta in small amounts** during gestation. The amount of neonatal **T4 is still low** compared to that in unaffected patients but is sufficient to initially prevent clinical manifestations of hypothyroidism.

As maternally derived neonatal T4 begins to wane in the first few weeks to months of life, classic symptoms of untreated hypothyroidism develop. Presenting signs include lethargy, hypotonia, constipation, and poor feeding. A hoarse cry, macroglossia, facial edema, and prolonged jaundice are also common.

(Choice A) Ectopic thyroid tissue typically produces decreased, not increased, T4.

(Choice B) Physiologically increased thyroid-binding globulin (TBG) levels in pregnancy result in

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of untreated hypothyroidism develop. Presenting signs include lethargy, hypotonia, constipation, and poor feeding. A hoarse cry, macroglossia, facial edema, and prolonged jaundice are also common.

(Choice A) Ectopic thyroid tissue typically produces decreased, not increased, T4.

(Choice B) Physiologically increased thyroid-binding globulin (TBG) levels in pregnancy result in increased total maternal T4 and triiodothyronine (T3) to maintain a euthyroid state. Because maternal levels of free T4 and T3 remain normal, the increase in maternal TBG does not affect the fetus.

(Choice C) Transplacental transfer of thyroid-stimulating antibodies in mothers with Graves disease results in transient neonatal hyperthyroidism (neonatal Graves disease). Laboratory findings would show increased T4 and decreased TSH.

(Choice E) TSH is a polypeptide hormone that does not cross the placenta.

Educational objective:
Congenital hypothyroidism, most commonly caused by abnormal thyroid gland development or location (ie, ectopy), is identified by elevated TSH and decreased thyroxine (T4) levels. Clinical manifestations of hypothyroidism are not present at birth due to the transplacental transfer of small amounts of maternal T4.

References

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A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin
- B. Cholecystokinin
- C. Glucagon
- D. Insulin
- E. Gastrin
- F. Growth hormone

Submit

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A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin (4%)
- ✓ B. Cholecystokinin (87%)
- C. Glucagon (2%)
- D. Insulin (2%)
- E. Gastrin (2%)
- F. Growth hormone (2%)

Correct

87% Answered correctly

31 secs Time Spent

01/30/2021 Last Updated

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The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland. Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells. Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin. Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells. Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones. Gallbladder stones form because of poor gallbladder contractility, which is secondary to inhibition of cholecystokinin release.

(Choices C and D) Somatostatin decreases the release of glucagon as well as insulin. However, the secretion of insulin is more profoundly inhibited than is glucagon; therefore, the net result is hyperglycemia.

(Choice A) Steatorrhea results from the decreased secretion of secretin as well as a decrease in gastrointestinal motility.

(Choice E) A decrease in gastrin release causes hypochlorhydria.

(Choice F) As indicated above, somatostatin does decrease growth hormone secretion from the normal pituitary gland, and it does so in growth-hormone-secreting pituitary adenomas. However, somatostatin cannot be used in clinical practice because of its extremely short half-life. Somatostatin analogs (octreotide

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secretion of insulin is more profoundly inhibited than is glucagon; therefore, the net result is hyperglycemia.

(Choice A) Steatorrhea results from the decreased secretion of secretin as well as a decrease in gastrointestinal motility.

(Choice E) A decrease in gastrin release causes hypochlorhydria.

(Choice F) As indicated above, somatostatin does decrease growth hormone secretion from the normal pituitary gland, and it does so in growth-hormone-secreting pituitary adenomas. However, somatostatin cannot be used in clinical practice because of its extremely short half-life. Somatostatin analogs (octreotide and lanreotide) have a longer plasma half-life and are available for clinical use.

Educational Objective:
Reduced gallbladder contractility, due to decreased cholecystokinin secretion, is responsible for biliary stones in patients with somatostatinoma.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gastrointestinal hormones
Subject	System	Topic

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A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

- A. Chronic autoimmune (Hashimoto) thyroiditis
- B. Graves disease
- C. Postpartum thyroiditis
- D. Secondary hyperthyroidism
- E. Secondary hypothyroidism
- F. Subacute granulomatous (de Quervain) thyroiditis

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months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

A. Chronic autoimmune (Hashimoto) thyroiditis (4%)
B. Graves disease (1%)
C. Postpartum thyroiditis (31%)
D. Secondary hyperthyroidism (2%)
✓ E. Secondary hypothyroidism (59%)
F. Subacute granulomatous (de Quervain) thyroiditis (1%)

Correct
59%
01 min
02/08/2021

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Central hypothyroidism	
Causes	• Mass lesions (eg, pituitary adenoma) • Pituitary surgery, trauma, irradiation • Infiltrative disorders (eg, sarcoidosis, hemochromatosis) • Pituitary infarction (eg, Sheehan syndrome)
Clinical features	• Hypothyroid symptoms • Mass-effect symptoms (eg, headache, visual field defects) if due to mass
Hormone levels	• Low free thyroxine (T4) • Low or inappropriately normal TSH • Other pituitary hormone deficiencies (eg, ACTH, prolactin, gonadotropins)

This patient has hypothyroidism manifesting as fatigue, hair loss, and brittle nails with a low serum thyroxine (T4) level. The **low TSH** confirms that this is due to hypothalamic-pituitary dysfunction (ie, **central/secondary hypothyroidism**) rather than a primary thyroid disorder, which would cause a compensatory rise in TSH. Central hypothyroidism is much less common than primary hypothyroidism. However, when it occurs, other hypothalamic-pituitary systems may be affected and patients may develop

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This patient has hypothyroidism manifesting as fatigue, hair loss, and brittle nails with a low serum thyroxine (T4) level. The **low TSH** confirms that this is due to hypothalamic-pituitary dysfunction (ie, **central/secondary hypothyroidism**) rather than a primary thyroid disorder, which would cause a compensatory rise in TSH. Central hypothyroidism is much less common than primary hypothyroidism. However, when it occurs, other hypothalamic-pituitary systems may be affected and patients may develop deficiencies of other pituitary hormones (eg, low gonadotropin levels leading to amenorrhea).

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders cause primary hypothyroidism with elevated TSH levels.

(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4 and suppressed TSH levels, typically with a goiter and ocular

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(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4 and suppressed TSH levels, typically with a goiter and ocular manifestations (eg, proptosis, lid lag).

(Choice D) Secondary (central) hyperthyroidism is a rare disorder, usually caused by a TSH-secreting pituitary adenoma. Both TSH and serum T4 levels are elevated.

(Choice F) Subacute granulomatous (de Quervain) thyroiditis causes a painful goiter and transient hyperthyroid symptoms; it typically follows a viral syndrome.

Educational objective:
Central hypothyroidism is characterized by low serum TSH and thyroxine (T4) levels and is due to hypothalamic-pituitary dysfunction. Sheehan syndrome is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. In addition to central hypothyroidism, patients may also develop deficiencies of other pituitary hormones (eg, ACTH, prolactin, gonadotropins).

References

- Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges.

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A 30-year-old woman comes to the office due to generalized weakness and paresthesia. Medical history is unremarkable and she takes no medications. However, the patient says her blood pressure was elevated at a workplace health fair 3 months ago, although she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine levels. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Sodium	Potassium	Bicarbonate
A.	High	Low	Low
B.	Low	High	Low
C.	Low	Low	High
D.	Normal	High	Low
E.	Normal	Low	High

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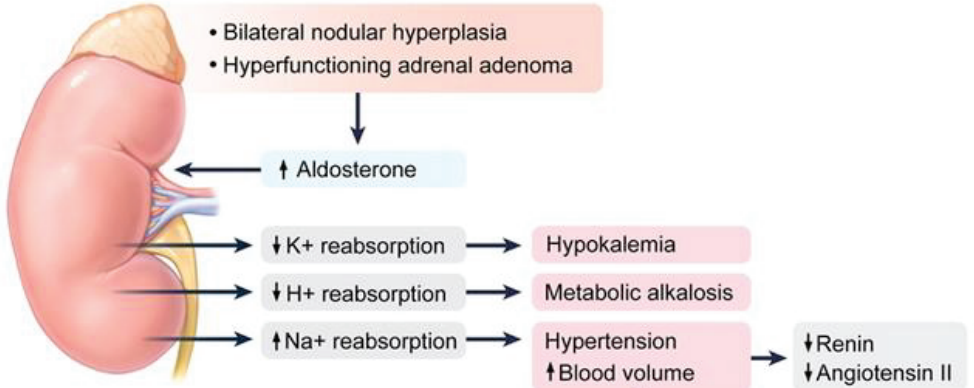
unremarkable and she takes no medications. However, the patient says her blood pressure was elevated at a workplace health fair 3 months ago, although she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine levels. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Sodium	Potassium	Bicarbonate	
A.	High	Low	Low	(51%)
B.	~~Low~~	~~High~~	~~Low~~	(9%)
C.	Low	Low	High	(2%)
D.	~~Normal~~	~~High~~	~~Low~~	(2%)
✓ E.	Normal	Low	High	(33%)

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Exhibit Display

Pathogenesis of primary hyperaldosteronism
(and aldosterone escape)



GFR = glomerular filtration rate.

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GFR = glomerular filtration rate.

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This patient has **hypertension** at a young age, suggesting a **secondary** cause. Her weakness and paresthesia indicate an associated electrolyte or acid-base disturbance. These findings, along with a suppressed plasma renin, suggest **primary mineralocorticoid excess (hyperaldosteronism)**. The most common causes of primary hyperaldosteronism include **unilateral adrenal adenoma** (Conn syndrome) and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), which can be differentiated on abdominal CT scan.

Hyperaldosteronism is characterized by increased Na^+ reabsorption in the renal collecting tubules. This creates a negative charge in the lumen, pulling K^+ and H^+ from tubular cells and leading to increased excretion of urinary K^+ and H^+. As a result, **hypokalemia** is common. Increased H^+ excretion by α-intercalated cells promotes bicarbonate production and increased activity of the basolateral HCO_3^-/Cl^- exchanger, resulting in elevated serum bicarbonate and **metabolic alkalosis**.

Despite the increase in Na^+ reabsorption, hypernatremia and pedal edema are rarely observed due to a phenomenon known as **aldosterone escape**. The increased intravascular volume causes increased renal blood flow (with resulting pressure natriuresis) and augmented release of atrial natriuretic peptide. This limits net sodium retention and prevents the development of overt volume overload and significant

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(Choice A) Due to aldosterone escape, serum Na^+ concentration is normal in hyperaldosteronism. Increased loss of K^+ and H^+ in the urine causes hypokalemia and high (not low) serum bicarbonate.

(Choice B) Patients with primary adrenal insufficiency have increased renal Na^+ loss and reduced urinary excretion of K^+ and H^+ due to low aldosterone activity. As a result, hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis develop. Hypovolemia also acts as a nonosmotic stimulus for antidiuretic hormone (ADH) secretion, further accentuating the hyponatremia.

(Choice C) Loop or thiazide diuretic use can cause hypovolemia, hyponatremia (mostly with thiazides), hypokalemia, and metabolic alkalosis due to urinary losses of Na^+, K^+, and H^+. Hypovolemia can also exacerbate hyponatremia (due to increased ADH secretion) and alkalosis (due to increased bicarbonate reabsorption).

(Choice D) Mineralocorticoid receptor antagonists (eg, spironolactone) block aldosterone receptors and impair urinary excretion of K^+ and H^+. Side effects include hyperkalemia and metabolic acidosis. Na^+ excretion is only mildly increased and serum Na^+ concentration is usually not significantly affected.

Educational objective:
Primary hyperaldosteronism causes increased Na^+ reabsorption in the renal collecting tubules, leading to increased urinary excretion of K^+ and H^+. Patients typically have secondary hypertension as well as

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hyperkalemia, and metabolic acidosis develop. Hypovolemia also acts as a nonosmotic stimulus for antidiuretic hormone (ADH) secretion, further accentuating the hyponatremia.

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Educational objective:
Primary hyperaldosteronism causes increased Na^+ reabsorption in the renal collecting tubules, leading to increased urinary excretion of K^+ and H^+. Patients typically have secondary hypertension as well as hypokalemia and metabolic alkalosis. The serum Na+ concentration remains normal due to aldosterone escape.

References

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A 54-year-old woman comes to the office for evaluation of elevated blood glucose. The patient was recently seen at an urgent care center, where she was found to have a nonfasting blood glucose level of 190 mg/dL. Medical history is insignificant, although she has not seen a physician for several years. She does not use tobacco or alcohol. BMI is 31.5 kg/m^2. Physical examination shows no abnormalities. Hemoglobin A1c is 8.5% and fasting plasma glucose level is 146 mg/dL. Recommendations for dietary modification and exercise are provided, and pharmacotherapy with metformin is planned. Which of the following laboratory tests should be obtained prior to starting this medication?

- A. Blood cell counts and mean corpuscular volume
- B. Oral glucose tolerance test
- C. Plasma lactate level
- D. Serum creatinine level
- E. Serum potassium level
- F. Serum TSH level

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recently seen at an urgent care center, where she was found to have a nonfasting blood glucose level of 190 mg/dL. Medical history is insignificant, although she has not seen a physician for several years. She does not use tobacco or alcohol. BMI is 31.5 kg/m^2. Physical examination shows no abnormalities. Hemoglobin A1c is 8.5% and fasting plasma glucose level is 146 mg/dL. Recommendations for dietary modification and exercise are provided, and pharmacotherapy with metformin is planned. Which of the following laboratory tests should be obtained prior to starting this medication?

A. Blood cell counts and mean corpuscular volume (2%)
B. Oral glucose tolerance test (1%)
C. Plasma lactate level (27%)
✓ D. Serum creatinine level (64%)
E. Serum potassium level (3%)
F. Serum TSH level (1%)

Correct
64%
45 secs
09/18/2020

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Metformin	
Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency

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Mechanism of action	• Inhibits mitochondrial glycerophosphate dehydrogenase & complex I • Upregulates AMP-activated protein kinase
Metabolic effects	• ↓ Hepatic glucose production • ↓ Intestinal glucose absorption • ↑ Peripheral glucose uptake/utilization • ↓ Lipogenesis
Pharmacokinetics	• Renal clearance • No significant metabolites
Adverse effects	• Diarrhea • Lactic acidosis • Vitamin B_{12} deficiency
Precautions/ contraindications	• Renal insufficiency (check serum creatinine) • Hepatic insufficiency • Congestive heart failure

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Metformin is the most commonly prescribed medication for type 2 diabetes mellitus. It **reduces hepatic gluconeogenesis** through multiple mechanisms, including inhibition of glycerophosphate dehydrogenase and complex I (the first enzymes in the electron transport chain) and upregulation of AMP-activated protein kinase. These mechanisms reduce the availability of substrates for gluconeogenesis (eg, dihydroxyacetone phosphate, pyruvate, fatty acids) and **increase peripheral glucose uptake** and utilization. Metformin does not increase endogenous insulin secretion and is therefore less likely to cause hypoglycemia than sulfonylureas or insulin.

The inhibition of gluconeogenic enzymes by metformin results in buildup of substrate molecules that are released into the plasma; decreased formation of pyruvate results in excess buildup of its precursor, lactate, which increases the risk of **lactic acidosis**. Although rare, the risk is increased in those with significant **renal dysfunction** or other disorders causing decreased lactate clearance (eg, hepatic impairment, congestive heart failure). For this reason, the glomerular filtration rate should be estimated using **serum creatinine measurement** prior to initiation of metformin therapy.

(Choice A) Metformin can cause vitamin B_{12} deficiency, likely due to decreased intestinal absorption. However, this is a chronic effect seen after long-term use, and preprescription testing is not needed.

(Choice B) The oral glucose tolerance test can be used for initial diagnosis of diabetes or primarily

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(Choice B) The oral glucose tolerance test can be used for initial diagnosis of diabetes or primarily gestational diabetes. This patient's diagnosis has been confirmed with the elevated fasting glucose and hemoglobin A1c; additional diagnostic testing is not necessary.

(Choice C) Plasma lactate levels are used to confirm acute lactic acidosis; measurement of a baseline level is not necessary.

(Choice E) Monitoring serum potassium is not necessary with metformin use. Serum potassium is routinely monitored with diuretics (especially loop diuretics), spironolactone, ACE inhibitors, and angiotensin II receptor blockers.

(Choice F) Thyroid function tests are not required for any antidiabetic medications, including metformin. They are routinely performed in patients taking lithium and amiodarone.

Educational objective:

Metformin inhibits hepatic gluconeogenesis and increases peripheral glucose utilization. Lactic acidosis is a rare complication of metformin therapy, but its risk is increased in patients with underlying renal insufficiency.

References

- Metformin-associated lactic acidosis: predisposing factors and outcome

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A newborn boy who was born at 39 weeks gestation by normal vaginal delivery has a serum TSH above the normal range and serum thyroxine (T4) below the normal range for his age. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital malformations. Which of the following is the most likely cause of this patient's condition?

A. Central hypothyroidism
B. Generalized thyroid hormone resistance
C. Reduced thyroid-binding globulin
D. Thyroid dysgenesis
E. TSH receptor–stimulating antibodies

Submit

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A newborn boy who was born at 39 weeks gestation by normal vaginal delivery has a serum TSH above the normal range and serum thyroxine (T4) below the normal range for his age. His mother has no medical conditions. On examination, the patient's length and weight are normal, and he has no apparent congenital malformations. Which of the following is the most likely cause of this patient's condition?

A. ~~Central hypothyroidism~~ (9%)
B. ~~Generalized thyroid hormone resistance~~ (11%)
C. Reduced thyroid-binding globulin (17%)
D. Thyroid dysgenesis (56%)
E. ~~TSH receptor–stimulating antibodies~~ (4%)

Correct

56% Answered correctly

50 secs Time Spent

09/18/2020 Last Updated

Explanation

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Congenital hypothyroidism		
Cause	**Free & total T4**	**TSH**
• Primary hypothyroidism ○ Thyroid dysgenesis ○ TSH resistance	↓	↑
• Thyroid hormone resistance	↑	↑
• Central hypothyroidism	↓	↓
• Transient due to maternal exposure ○ Iodine excess or deficiency ○ TSH receptor–blocking antibodies ○ Antithyroid medications	↓	↑

T4 = thyroxine.

This patient has **primary hypothyroidism**, a congenital condition most commonly caused by **thyroid dysgenesis**. Thyroid dysgenesis refers to an underdeveloped thyroid (ie, **hypoplasia**, **aplasia**) or an

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This patient has **primary hypothyroidism**, a congenital condition most commonly caused by **thyroid dysgenesis**. Thyroid dysgenesis refers to an underdeveloped thyroid (ie, **hypoplasia**, **aplasia**) or an ectopic thyroid, which can lie anywhere along the normal path of embryologic descent from the base of the tongue to its normal location anterior to the thyroid cartilage. Most cases are sporadic and isolated without other congenital abnormalities.

Newborns are usually asymptomatic due to the transplacental transfer of maternal thyroxine (T4), although levels are decreased compared to those of healthy patients. Because of insufficient feedback inhibition from **low T4** levels, **TSH** is **elevated**. Newborn screening allows for early identification and treatment with levothyroxine, which prevents the development of neurocognitive dysfunction.

(Choice A) Hypothalamic or pituitary dysfunction can lead to central hypothyroidism due to deficient TSH production. TSH and T4 levels would both be low.

(Choice B) Congenital hypothyroidism can also be caused by thyroid hormone resistance (eg, thyroid hormone receptor mutations). However, TSH and T4 levels would be elevated due to impaired thyroid hormone feedback.

(Choice C) Thyroid-binding globulin (TBG) is a transport protein that binds T4. TBG deficiency results in a

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(Choice B) Congenital hypothyroidism can also be caused by thyroid hormone resistance (eg, thyroid hormone receptor mutations). However, TSH and T4 levels would be elevated due to impaired thyroid hormone feedback.

(Choice C) Thyroid-binding globulin (TBG) is a transport protein that binds T4. TBG deficiency results in a euthyroid state characterized by a low level of total T4 but normal TSH and free T4 levels.

(Choice E) Neonatal Graves disease is characterized by the transplacental transfer of maternal TSH receptor–stimulating antibodies due to maternal Graves disease. This condition causes transient hyperthyroidism with elevated T4 and decreased TSH.

Educational objective:

Thyroid dysgenesis (ie, hypoplasia, aplasia, ectopy) is the most common cause of primary congenital hypothyroidism. In this condition, TSH is elevated and thyroxine (T4) is low.

References

- Congenital hypothyroidism.

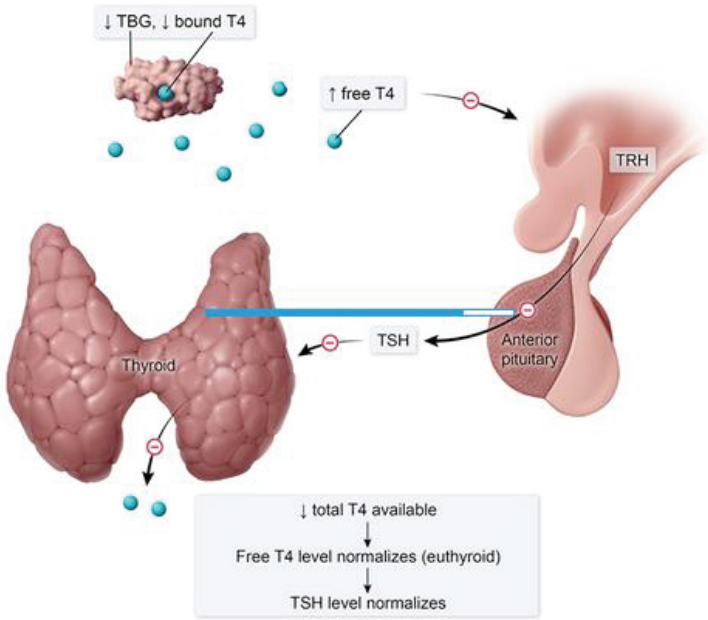
Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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Exhibit Display

Thyroxine-binding globulin (TBG) deficiency



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A 40-year-old man comes to the office due to recurrent epigastric abdominal pain, nausea, and watery diarrhea for the past several months. The patient has had similar burning pain previously and was treated for peptic ulcer disease. He has been taking over-the-counter antacids but with no significant symptom relief. The patient does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Abdominal examination shows mild epigastric tenderness and increased bowel sounds. Testing for stool occult blood is positive, and laboratory studies show microcytic hypochromic anemia. Serum gastrin level is markedly elevated. Upper gastrointestinal endoscopy reveals prominent gastric folds and multiple ulcers in the duodenum and proximal jejunum. Given these findings, this patient should be assessed for a personal or family history of which of the following conditions?

A. Cerebellar hemangioblastomas
B. Mucosal neuromas
C. Plexiform neurofibromas
D. Recurrent nephrolithiasis
E. Thyroid malignancy

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for peptic ulcer disease. He has been taking over-the-counter antacids but with no significant symptom relief. The patient does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Abdominal examination shows mild epigastric tenderness and increased bowel sounds. Testing for stool occult blood is positive, and laboratory studies show microcytic hypochromic anemia. Serum gastrin level is markedly elevated. Upper gastrointestinal endoscopy reveals prominent gastric folds and multiple ulcers in the duodenum and proximal jejunum. Given these findings, this patient should be assessed for a personal or family history of which of the following conditions?

A. Cerebellar hemangioblastomas (5%)
B. Mucosal neuromas (16%)
C. Plexiform neurofibromas (7%)
D. Recurrent nephrolithiasis (37%)
E. Thyroid malignancy (33%)

Correct

37%

01 min, 08 secs

08/25/2020

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Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient's recurrent peptic ulcer disease, associated with chronic blood loss (iron deficiency) anemia

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This patient's recurrent peptic ulcer disease, associated with chronic blood loss (iron deficiency) anemia and an elevated gastrin level, is likely due to a gastrin-secreting pancreatic tumor (**Zollinger-Ellison syndrome**). Although most gastrinomas are sporadic, 20%-30% occur in association with **multiple endocrine neoplasia type 1** (MEN1). This autosomal dominant disorder is most often due to mutations of the *MEN1* gene (menin protein) and is characterized by **p**arathyroid adenomas, **p**ituitary tumors, and **p**ancreatic endocrine tumors (the **3 Ps**).

Patients with Zollinger-Ellison syndrome or other pancreatic neuroendocrine tumors should be assessed for symptoms or family history of other MEN1 manifestations. Potential associated conditions include **primary hyperparathyroidism** (eg, hypercalcemia, constipation, **kidney stones**) and pituitary adenomas (eg, headaches, visual field defects).

(Choices A and C) Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder characterized by multiple tumors, including hemangioblastomas, pheochromocytoma, and renal cell carcinoma. Plexiform neurofibromas are large aggregates of neuronal cells, supporting cells, and connective tissue that are seen in approximately 30% of patients with neurofibromatosis type 1 (NF1). Although an increased incidence of pancreatic endocrine tumors has been reported in both VHL and NF1, these associations are much less frequent than in MEN1.

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pancreatic endocrine tumors has been reported in both VHL and NF1, these associations are much less frequent than in MEN1.

(Choices B and E) MEN2A consists of medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. MEN2B (also known as MEN3) is associated with medullary thyroid cancer, pheochromocytoma, mucosal neuromas, and a marfanoid habitus. The MEN2 syndromes are not associated with pancreatic endocrine tumors.

Educational objective:

Multiple endocrine neoplasia type 1 consists of hyperparathyroidism (eg, hypercalcemia, constipation, kidney stones), pituitary tumors, and pancreatic endocrine tumors (eg, gastrinoma). The genetic defect involves mutations of the *MEN1* gene.

References

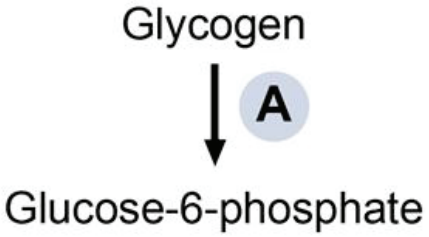
- Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1).

Pathology	Endocrine, Diabetes & Metabolism	Multiple endocrine neoplasia
Subject	System	Topic

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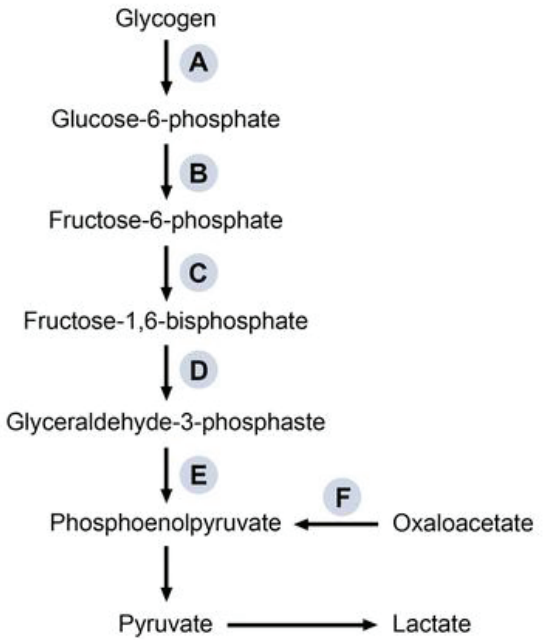
A 34-year-old woman is brought to the emergency department in the early morning with confusion, tremor, and sweating. Her husband reports that she did not wake to her alarm clock and was difficult to arouse. Over the past week, the patient has had similar episodes in the morning before eating and after exercise. Past medical history is unremarkable. Blood pressure is 135/95 mm Hg, pulse is 110/min, and respirations are 24/min. The patient is arousable to voice but does not follow commands. Cranial nerve examination, muscle tone, and deep tendon reflexes are normal. A bedside fingerstick glucose level is 35 mg/dL. The patient is given an intravenous infusion of glucose, which rapidly improves her mental status. Further evaluation reveals that her episodes of hypoglycemia are due to increased levels of an endogenous hormone. This hormonal imbalance is most likely causing the patient's symptoms by stimulating which of the following conversions?



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Glycogen

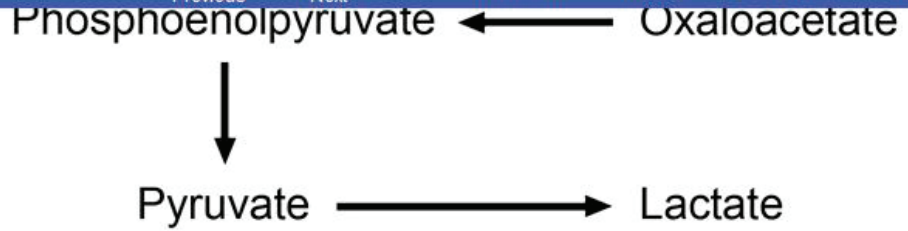
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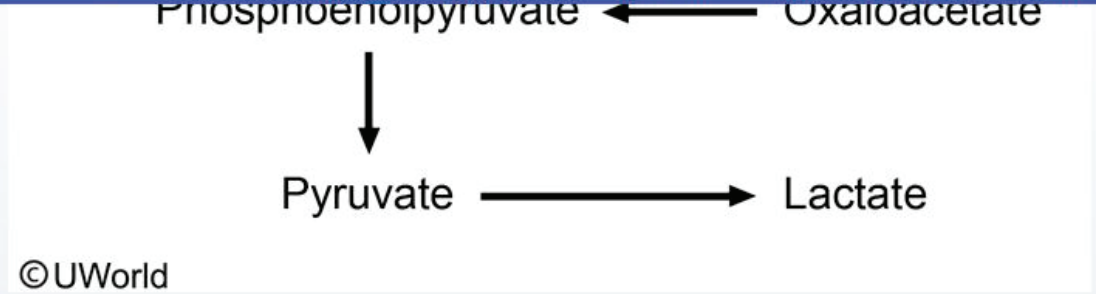


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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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- A. A (20%)
- B. B (9%)
- C. C (43%)
- D. D (5%)
- E. E (3%)
- F. F (18%)

Incorrect
Correct answer

43%

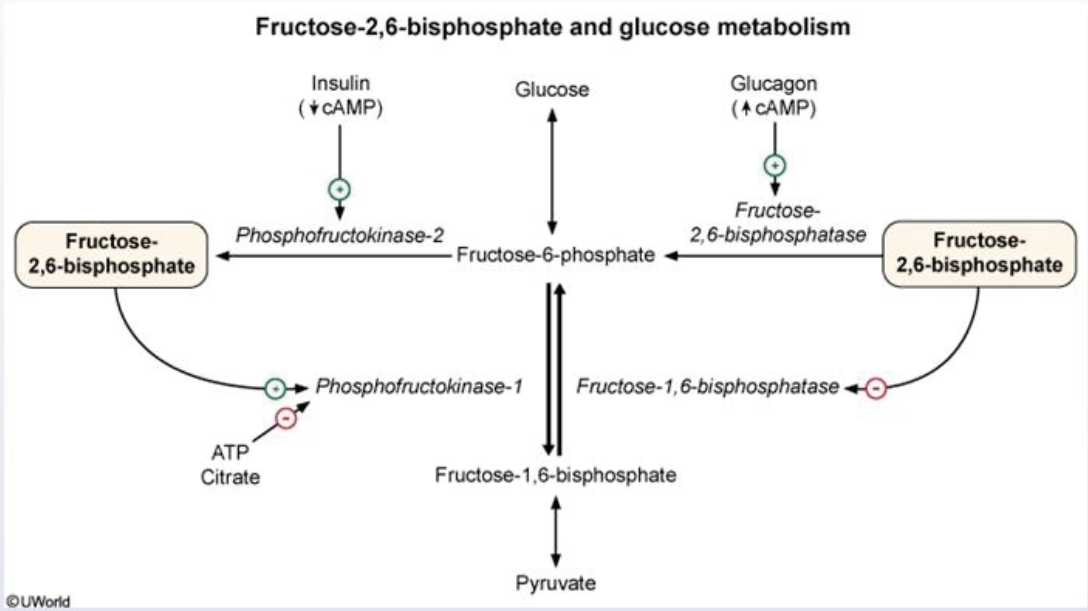
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Explanation



This patient has developed **hypoglycemia** secondary to **increased levels of an endogenous hormone**. Hypoglycemia can develop due to **insulin excess** (either endogenous [eg, insulinoma] or exogenous [eg,

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This patient has developed **hypoglycemia** secondary to **increased levels of an endogenous hormone**. Hypoglycemia can develop due to **insulin excess** (either endogenous [eg, insulinoma] or exogenous [eg, inadvertent overdose, surreptitious insulin/secretagogue use]) as well as deficiency of counterregulatory hormones (eg, glucagon, epinephrine, cortisol).

Insulin lowers plasma glucose by increasing glucose uptake in fat, muscle, and liver. In addition, insulin causes an **increase in glycolysis** by **activating** phosphofructokinase-2 (**PFK2**), the enzyme that produces fructose 2,6-bisphosphate. The intracellular concentration of fructose 2,6-bisphosphate is the major regulator of phosphofructokinase-1 (**PFK1**), which **converts fructose 6-phosphate** to **fructose 1,6-bisphosphate** in the rate-limiting step of glycolysis. Fructose 2,6-bisphosphate stimulates PFK1 while inhibiting the reverse enzyme, fructose 1,6-bisphosphatase. As a result, the rise in fructose 2,6-bisphosphate levels caused by insulin leads to an increase in glycolysis and inhibition of gluconeogenesis, with a corresponding **decrease** in circulating **glucose levels**.

(Choice A) Insulin promotes the storage of glucose by *inhibiting* glycogen phosphorylase (breaks down glycogen into glucose-6-phosphate) and stimulating glycogen synthase (incorporates UDP-glucose into glycogen).

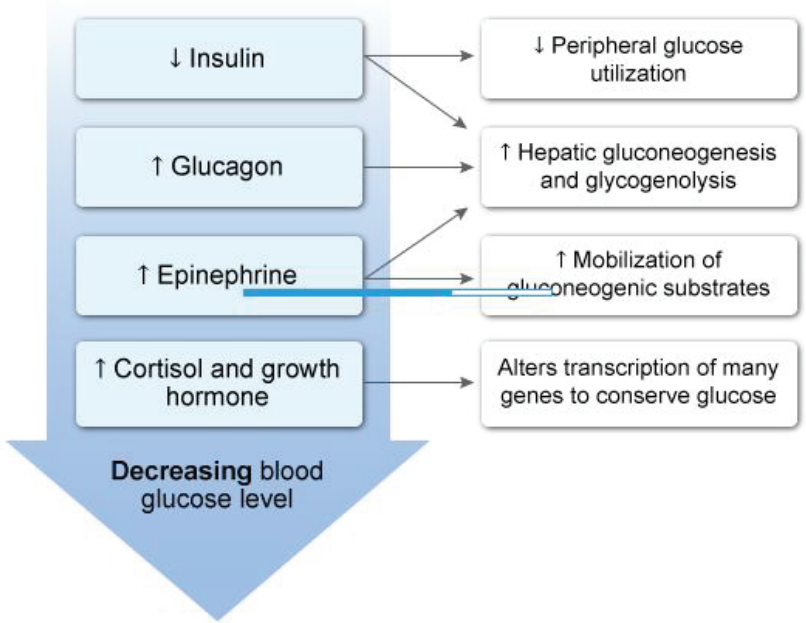
(Choices B, D, and E) Glucose 6-phosphate is converted to fructose 6-phosphate by phosphoglucose

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Physiologic defense against hypoglycemia



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(Choices B, D, and E) Glucose 6-phosphate is converted to fructose 6-phosphate by phosphoglucose

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glycogen into glucose-6-phosphate) and stimulating glycogen synthase (incorporates UDP-glucose into glycogen).

(Choices B, D, and E) Glucose 6-phosphate is converted to fructose 6-phosphate by phosphoglucose isomerase. Fructose 1,6-bisphosphate is converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by fructose bisphosphate aldolase. Glyceraldehyde 3-phosphate is converted to phosphoenolpyruvate through the action of multiple enzymes. These steps are readily reversible and not regulated by insulin.

(Choice F) Oxaloacetate is converted to phosphoenolpyruvate by phosphoenolpyruvate carboxykinase during gluconeogenesis; this reaction is *downregulated* by high insulin levels.

Educational objective:
Phosphofructokinase-1 (PFK1) catalyzes the rate-limiting step in glycolysis, and the most potent stimulator of PFK1 is fructose 2,6-bisphosphate. Insulin increases production of fructose 2,6-bisphosphate by phosphofructokinase-2 (PFK2), thereby stimulating glycolysis.

References

- Roles for fructose-2,6-bisphosphate in the control of fuel metabolism: beyond its allosteric effects on glycolytic and gluconeogenic enzymes.

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An individual with a point mutation affecting the gene responsible for neurophysin synthesis is most likely to suffer from:

A. Short stature
B. Hyperpigmentation
C. Diabetes insipidus
D. Hypothyroidism
E. Infertility

Submit

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An individual with a point mutation affecting the gene responsible for neurophysin synthesis is most likely to suffer from:

A. Short stature (8%)
B. Hyperpigmentation (11%)
C. Diabetes insipidus (69%)
D. Hypothyroidism (4%)
E. Infertility (5%)

Correct

69%
Answered correctly

30 secs
Time Spent

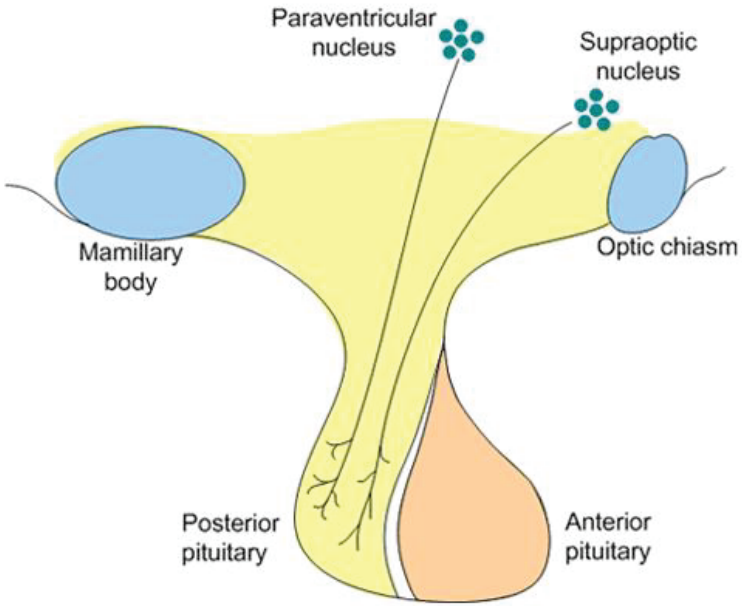
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Explanation

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produced within the paraventricular and supraoptic nuclei, respectively, and released from the posterior

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Neurophysins are carrier proteins for oxytocin and vasopressin (antidiuretic hormone, ADH), hormones produced within the paraventricular and supraoptic nuclei, respectively, and released from the posterior pituitary. Like the hormones they accompany, neurophysins are produced within the neuronal cell bodies of hypothalamic nuclei. Neurophysins bind oxytocin and vasopressin and act as chaperone molecules as they are shuttled toward the nerve terminals in the posterior pituitary.

Neurophysin II has a binding site specific for vasopressin and is thought to be involved in the transport and packaging of vasopressin through the endoplasmic reticulum (ER) and Golgi apparatus into neurosecretory granules. A point mutation in neurophysin II could result in abnormal protein folding and removal from the ER along with bound vasopressin, thereby decreasing availability of vasopressin for neurosecretory release. Such a mechanism may be responsible for some cases of autosomal dominant hereditary hypothalamic diabetes insipidus.

(Choice A) Short stature may result from a growth hormone deficiency. Neither hypothalamic GHRH release nor anterior pituitary growth hormone secretion involves neurophysins.

(Choice B) Generalized hyperpigmentation is a manifestation of Addison's disease, where a primary defect in adrenal cortisol production reduces feedback inhibition of anterior pituitary pro-opiomelanocortin (POMC)

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release for anterior pituitary growth hormone secretion involves neurophysins.

(Choice B) Generalized hyperpigmentation is a manifestation of Addison's disease, where a primary defect in adrenal cortisol production reduces feedback inhibition of anterior pituitary pro-opiomelanocortin (POMC) synthesis. As a result, POMC cleavage products, including ACTH and melanocyte-stimulating hormone (MSH), are secreted in excess. High MSH levels cause increased melanin synthesis by melanocytes.

(Choice D) The synthesis and release of TRH and TSH do not involve neurophysins. TRH stimulates the release of both TSH and prolactin. Dopamine tonically inhibits prolactin release.

(Choice E) Infertility can result from inadequate hypothalamic release of GnRH or decreased anterior pituitary production of FSH or LH.

Educational Objective:
Neurophysins are carrier proteins for oxytocin and vasopressin (ADH). Oxytocin and vasopressin are carried by unique neurophysins from their site of production in the cell bodies of the paraventricular and supraoptic nuclei to their site of release in the axon terminals of the posterior pituitary. Point mutations in neurophysin II underlie most cases of hereditary hypothalamic diabetes insipidus, a disorder resulting from insufficient ADH release into the systemic circulation.

Physiology Endocrine, Diabetes & Metabolism Diabetes insipidus

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A 30-year-old man comes to the office with a neck lump. The patient is otherwise asymptomatic and discovered the nodule incidentally while showering. His medical history is significant for a recently diagnosed pheochromocytoma, which was successfully removed. The patient's father died of thyroid cancer in his 30s. An ultrasound reveals a hypoechoic 3-cm nodule in the right lobe of the thyroid gland. Fine-needle biopsy of the nodule is consistent with a subtype of thyroid cancer. The patient undergoes total thyroidectomy with central neck dissection. Which of the following is the most likely histological finding?

A. Branching structures with interspersed calcified bodies
B. Follicular hyperplasia with tall cells forming intrafollicular projections
C. Nests of polygonal cells with Congo red-positive deposits
D. Pleomorphic giant cell nests with occasional multinucleated cells
E. Sheets of uniform cells forming small follicles

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A 30-year-old man comes to the office with a neck lump. The patient is otherwise asymptomatic and discovered the nodule incidentally while showering. His medical history is significant for a recently diagnosed pheochromocytoma, which was successfully removed. The patient's father died of thyroid cancer in his 30s. An ultrasound reveals a hypoechoic 3-cm nodule in the right lobe of the thyroid gland. Fine-needle biopsy of the nodule is consistent with a subtype of thyroid cancer. The patient undergoes total thyroidectomy with central neck dissection. Which of the following is the most likely histological finding?

A. ~~Branching structures with interspersed calcified bodies~~ (13%)

B. ~~Follicular hyperplasia with tall cells forming intrafollicular projections~~ (11%)

✓ C. Nests of polygonal cells with Congo red-positive deposits (58%)

D. Pleomorphic giant cell nests with occasional multinucleated cells (6%)

E. ~~Sheets of uniform cells forming small follicles~~ (9%)

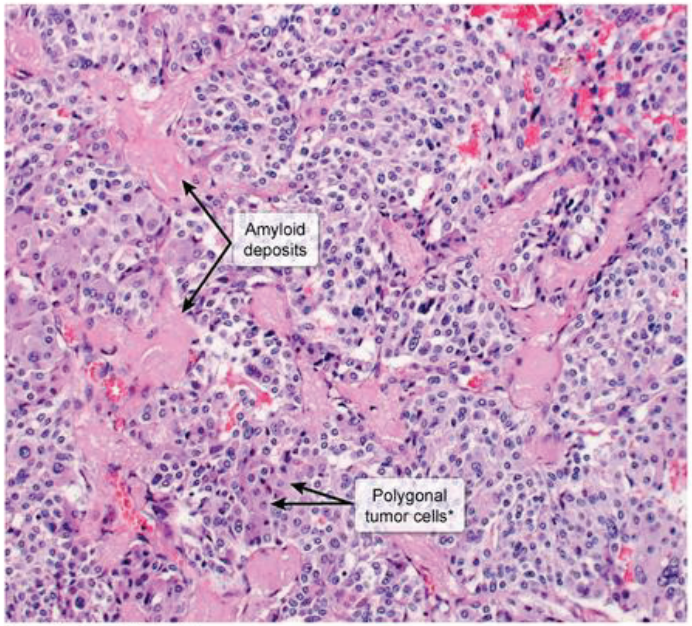
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Medullary thyroid carcinoma



*Derived from C (parafollicular) cells

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This patient has a personal history of pheochromocytoma and a family history of thyroid cancer. His new thyroid malignancy therefore raises suspicion for **multiple endocrine neoplasia type 2** (MEN2), which is characterized by:

- **Medullary thyroid cancer**
- Pheochromocytoma
- Either parathyroid hyperplasia (type 2A) or marfanoid habitus and mucosal neuromas (type 2B)

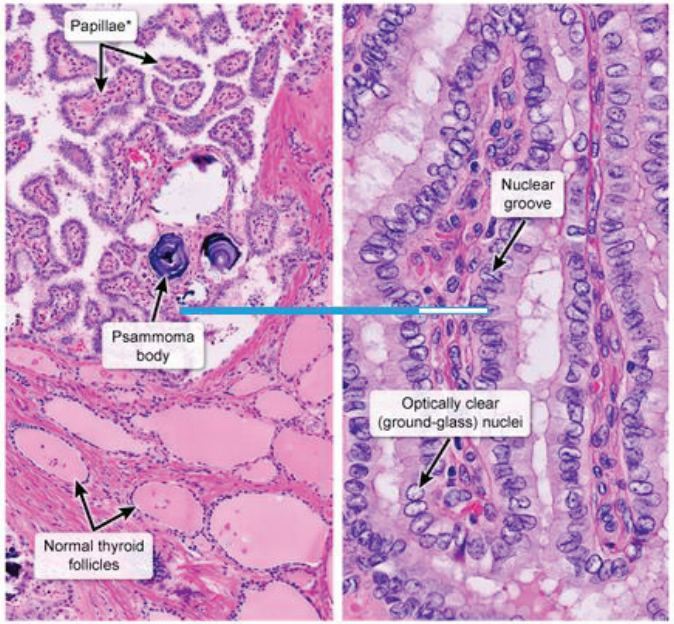
Approximately 20% of medullary thyroid cancers are familial, occurring as part of MEN2 or familial medullary thyroid cancer syndrome due to germ-line mutations of the RET proto-oncogene. Medullary thyroid cancer is a neuroendocrine tumor that arises from **parafollicular calcitonin-secreting C cells**. Nests or sheets of polygonal or spindle-shaped cells with extracellular **amyloid** deposits are seen microscopically. These amyloid deposits are derived from calcitonin secreted by the neoplastic C cells and stain with **Congo red**. Despite overproduction of calcitonin, hypocalcemia is not a prominent feature.

(Choice A) Gross inspection of papillary thyroid cancer may reveal formation of visible papillae; microscopic inspection of papillae shows a fibrovascular core, often with laminar calcifications (psammoma bodies). The cells contain pale nuclei with finely dispersed chromatin, giving them an empty or ground-glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to

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Papillary thyroid carcinoma



*Fibrovascular cores lined by epithelial cells

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glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to

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glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to invagination of the nuclear membrane.

(Choice B) Hyperplastic follicles with tall, crowded cells forming intrafollicular projections can be seen in Graves disease, often with hyperactive resorption of colloid leading to scalloping of the colloid edges.

(Choice D) Anaplastic thyroid cancer is an aggressive tumor with a very poor prognosis. It is most common in older patients (age >60). Cytologic features include markedly pleomorphic cells, including irregular giant cells and biphasic spindle cells.

(Choice E) The presence of colloid-containing microfollicles suggests a benign follicular adenoma. Follicular carcinoma can also contain small follicles but will show vascular or capsular invasion.

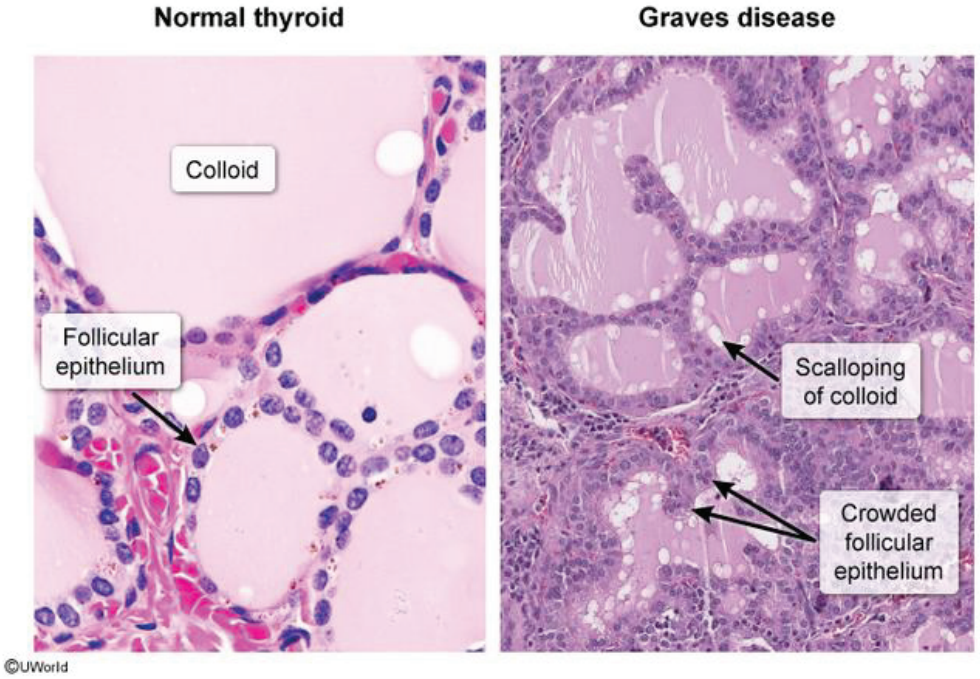
Educational objective:
Medullary thyroid cancer is a neuroendocrine tumor that arises from parafollicular calcitonin-secreting C cells. It is characterized by nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits derived from calcitonin.

Pathology	Endocrine, Diabetes & Metabolism	Thyroid cancer
Subject	System	Topic

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glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to

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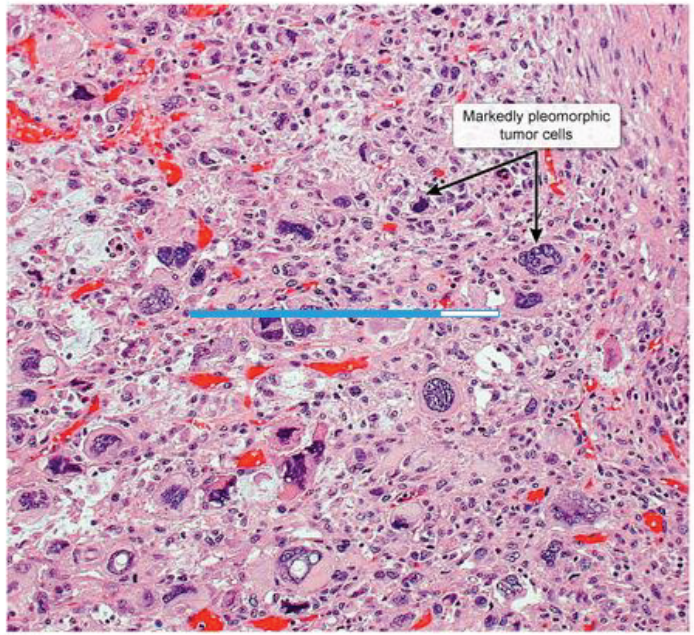
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glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to

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Anaplastic thyroid carcinoma



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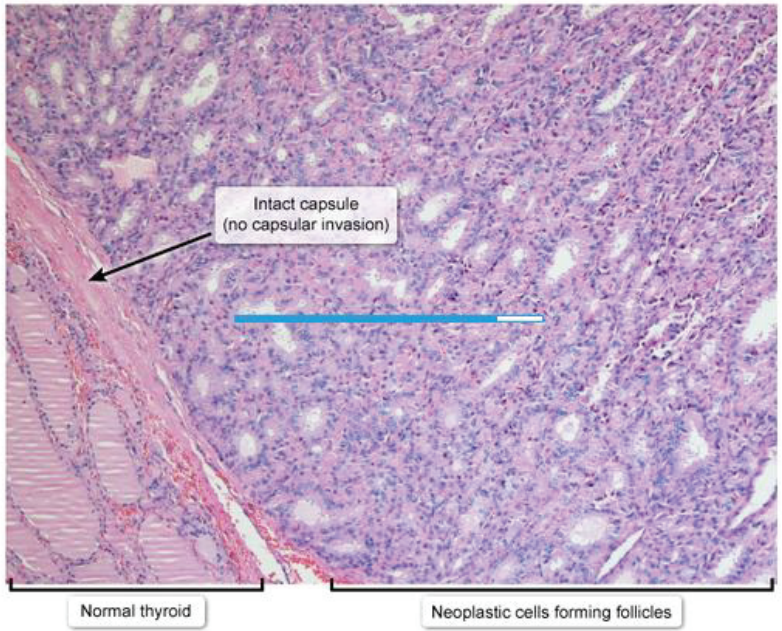
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glass appearance (Orphan Annie eye nuclei). Intranuclear inclusions and grooves can be seen due to

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Follicular adenoma



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A 46-year-old woman comes to the office with a painful rash involving her groin and legs that has been worsening over the last 2 weeks. She was diagnosed with diabetes mellitus 6 months ago but has no other medical problems other than occasional loose stools. Physical examination shows coalescing erythematous plaques with crusting and scaling at the borders and central areas of brownish induration. Biopsy of the lesions reveals superficial necrolysis. Which of the following laboratory abnormalities is most likely to be present in this patient?

A. Elevated amino acids
B. Elevated gastrin
C. Elevated glucagon
D. Elevated somatostatin
E. Elevated vasoactive intestinal polypeptide
F. Low insulin
G. Low zinc

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worsening over the last 2 weeks. She was diagnosed with diabetes mellitus 6 months ago but has no other medical problems other than occasional loose stools. Physical examination shows coalescing erythematous plaques with crusting and scaling at the borders and central areas of brownish induration. Biopsy of the lesions reveals superficial necrolysis. Which of the following laboratory abnormalities is most likely to be present in this patient?

A. Elevated amino acids (3%)
B. Elevated gastrin (2%)
C. Elevated glucagon (30%)
D. Elevated somatostatin (4%)
E. Elevated vasoactive intestinal polypeptide (9%)
F. Low insulin (10%)
G. Low zinc (38%)

Correct

30%
Answered correctly

52 secs
Time Spent

09/03/2020
Last Updated

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Features of glucagonoma	
Clinical presentation	• **Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum & extremities • Lesions enlarge & coalesce, leaving a central indurated area with peripheral blistering & scaling • **Diabetes mellitus**/hyperglycemia • Gastrointestinal symptoms (diarrhea, anorexia, abdominal pain)
Diagnosis	• Markedly elevated glucagon levels

This patient most likely has a **glucagonoma**, a rare tumor arising from the **alpha cells** of the pancreatic islets of Langerhans. Glucagonomas secrete large quantities of glucagon, so affected patients often have **hyperglycemia** or overt **diabetes mellitus**. A characteristic skin finding is **necrolytic migratory erythema**, an elevated painful and pruritic rash typically affecting the face, groin, and extremities. Over time, small erythematous papules coalesce to form large, indurated plaques with a central clearing that often appears brown or bronze-colored. Diagnosis is made by detecting elevated levels of **glucagon** in the serum.

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serum.

(Choice A) Glucagon acts on the liver to promote amino acid oxidation and gluconeogenesis from amino acids. Circulating levels of amino acids are low in glucagonoma and thought to contribute to development of necrolytic migratory erythema.

(Choice B) Elevated gastrin levels in patients with gastrinoma are associated with hypersecretion of gastric acid and resultant gastrointestinal ulceration. The peptic ulcers that occur with gastrinomas are often in unusual areas, such as the jejunum. Patients with gastrinomas can also have diarrhea and abdominal pain.

(Choice D) Excess somatostatin secretion from a somatostatinoma typically presents with abdominal pain, gallbladder stones, constipation, hyperglycemia, and steatorrhea. These manifestations result from somatostatin-induced inhibition of insulin, glucagon, gastrin, secretin, and cholecystokinin secretion, and inhibition of gastrointestinal motility.

(Choice E) High levels of vasoactive intestinal polypeptide (VIP) are seen in patients with a VIPoma, which typically presents with intractable diarrhea, hypokalemia, and achlorhydria. Patients are usually hypotensive due to dehydration and the vasodilatory effects of VIP.

(Choice F) Diabetes mellitus is present in the majority of patients with glucagonoma, most likely due to

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hypotensive due to dehydration and the vasodilatory effects of VIP.

(Choice F) Diabetes mellitus is present in the majority of patients with glucagonoma, most likely due to excessive hepatic glucose production. Insulin levels tend to be normal but can be elevated secondary to hyperglycemia and glucagon-induced stimulation of the pancreatic beta cells.

(Choice G) Zinc deficiency causes erythematous skin lesions (mainly around body orifices) that are predominantly vesicular and pustular. Other features include hypogonadism, impaired taste and smell, night blindness, and impaired wound healing. Although the skin lesions in zinc deficiency can resemble necrolytic migratory erythema, this patient's lack of additional findings and her recent diabetes mellitus diagnosis make glucagonoma more likely.

Educational objective:
Glucagonoma presents with hyperglycemia (often as newly diagnosed diabetes mellitus) and necrolytic migratory erythema (blistering erythematous plaques with central clearing) affecting the groin, face, and extremities. The diagnosis is made by detecting elevated glucagon levels.

References

- The glucagonoma syndrome. Clinical and pathologic features in 21 patients.

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www.ncbi.nlm.nih.gov/pubmed/8606627

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A 7-year-old boy is being evaluated for growth retardation. Brain MRI shows a 4 cm multiloculated, cystic, suprasellar lesion, which is bulging into the floor of the third ventricle and base of the brain. Calcifications are present. From which of the following structures is this mass most likely derived?

A. Prolactin secreting cells of the anterior pituitary
B. Remnants of the Rathke pouch
C. Astrocytes
D. Arachnoid cap cells
E. Posterior pituitary cells

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A 7-year-old boy is being evaluated for growth retardation. Brain MRI shows a 4 cm multiloculated, cystic, suprasellar lesion, which is bulging into the floor of the third ventricle and base of the brain. Calcifications are present. From which of the following structures is this mass most likely derived?

A. Prolactin secreting cells of the anterior pituitary (6%)
B. Remnants of the Rathke pouch (80%)
C. Astrocytes (7%)
D. Arachnoid cap cells (2%)
E. Posterior pituitary cells (3%)

Correct

80% Answered correctly

29 secs Time Spent

11/22/2020 Last Updated

Explanation

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Craniopharyngiomas are tumors arising from remnants of Rathke's pouch. The anterior pituitary is formed from an out-pouching of the pharyngeal roof and is called Rathke's pouch. The posterior pituitary gland arises from an extension of the hypothalamic neurons. Together, the anterior and posterior pituitary glands lie in the sella turcica at the skull base.

During the time of pituitary development, remnants of Rathke's pouch cells can remain in the diencephalon (the posterior region of the forebrain). Neoplastic transformation of these "pouch cells" is called a craniopharyngioma. Typically, craniopharyngiomas have three components: solid, comprised of the actual tumor cells; cystic, filled with "machinery oil" liquid; and a calcified component. Any suprasellar mass with three components is highly suggestive of craniopharyngioma. Craniopharyngioma symptoms include headaches, visual field defects, and hypopituitarism, evidenced by the growth retardation of this child. Ultimately, compression of the pituitary stalk by craniopharyngioma leads to hyperprolactinemia by loss of dopaminergic inhibition. Craniopharyngiomas are usually tumors of childhood, being most frequently discovered between the ages of 5 and 10 years of age.

(Choice A) Prolactinomas are uncommon in young children. They typically appear as a homogenous mass when imaged.

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(Choice A) Prolactinomas are uncommon in young children. They typically appear as a homogenous mass when imaged.

(Choice C) Gliomas can occur in the suprasellar region if they arise from the optic apparatus, but do not appear on imaging with the three components described above. Gliomas typically presents with visual symptoms, hypothalamic dysfunction, and hypopituitarism.

(Choice D) Meningiomas are tumors of the leptomeninges, which is the lining of the brain. Hence, meningiomas can occur in any "lined" part of the brain including sellar and suprasellar regions. Meningiomas are usually homogeneous appearance on MRI and can be seen "sticking" to leptomeninges.

Educational Objective:

1. The anterior pituitary is formed from an out-pouching of the pharyngeal roof and is called Rathke's pouch. The posterior pituitary gland arises from an extension of the hypothalamic neurons.
2. Craniopharyngiomas are tumors arising from Rathke's pouch remnants in the anterior pituitary. They characteristically have three components: solid, cystic, and calcified. They present during childhood, usually, with mass effect and visual deficits.

Pathology Endocrine, Diabetes & Metabolism Craniopharyngiomas

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A 53-year-old woman comes to the physician for a routine check-up. She has no current complaints. Her past medical history is significant for osteoarthritis of the right knee. Her mother suffered from hypertension and was diagnosed with breast cancer at age 68, from which she died 4 years later. Her father had diabetes mellitus and died in a motor vehicle accident at age 56. The patient's blood pressure is 140/85 mm Hg and heart rate is 80/min. Physical examination is normal. Laboratory testing is significant for a fasting blood glucose level of 140 mg/dL on more than 2 occasions. This patient is most likely to die from which of the following conditions?

A. Breast cancer
B. Hyperosmolar nonketotic coma
C. Myocardial infarction
D. Renal failure
E. Stroke

Submit

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A 53-year-old woman comes to the physician for a routine check-up. She has no current complaints. Her past medical history is significant for osteoarthritis of the right knee. Her mother suffered from hypertension and was diagnosed with breast cancer at age 68, from which she died 4 years later. Her father had diabetes mellitus and died in a motor vehicle accident at age 56. The patient's blood pressure is 140/85 mm Hg and heart rate is 80/min. Physical examination is normal. Laboratory testing is significant for a fasting blood glucose level of 140 mg/dL on more than 2 occasions. This patient is most likely to die from which of the following conditions?

A. Breast cancer (6%)
B. Hyperosmolar nonketotic coma (3%)
C. Myocardial infarction (61%)
D. Renal failure (23%)
E. Stroke (5%)

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Risk factors for coronary heart disease	
Highest risk factors (coronary heart disease equivalents)	• Noncoronary atherosclerotic disease • Diabetes mellitus • Chronic kidney disease
Major risk factors	• Hypertension • Hyperlipidemia (↑LDL & triglycerides) • Cigarette smoking • Advanced age • Obesity • Physical inactivity

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Several studies have shown that diabetes mellitus is one of the strongest risk factors for coronary heart disease. Cardiovascular mortality is increased by 2- to 4-fold in patients with type 2 diabetes mellitus, and approximately 40% of patients die secondary to coronary heart disease. For a person with type 2 diabetes mellitus, the risk of dying from coronary heart disease exceeds the risk of dying from any of the other listed causes, even in the absence of other major risk factors for coronary heart disease.

(Choice A) The risk of breast cancer is not increased in patients with diabetes mellitus. Although this

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mellitus, the risk of dying from coronary heart disease exceeds the risk of dying from any of the other listed causes, even in the absence of other major risk factors for coronary heart disease.

(Choice A) The risk of breast cancer is not increased in patients with diabetes mellitus. Although this patient has a family history of breast cancer, her risk is not significantly increased since her mother was at an advanced age when the cancer occurred.

(Choice B) Diabetic ketoacidosis (DKA) and hyperosmolar coma are acute complications of untreated diabetes mellitus. Hyperosmolar coma is seen mainly with type 2 diabetes mellitus and is characterized by very high blood sugar levels without ketoacidosis. The mortality of hyperosmolar coma is higher than DKA; however, very few patients with diabetes die directly from DKA or hyperosmolar coma.

(Choice D) Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), followed by hypertension. However, approximately 50% of patients with ESRD die due to cardiovascular disease, with infections being the next most common cause.

(Choice E) The risk of stroke is increased in patients with diabetes mellitus. However, cerebrovascular accidents account for about 10% of total mortality in patients with type 2 diabetes mellitus versus 40% from coronary heart disease.

Educational objective:

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however, very few patients with diabetes die directly from DKA or hyperosmolar coma.

(Choice D) Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), followed by hypertension. However, approximately 50% of patients with ESRD die due to cardiovascular disease, with infections being the next most common cause.

(Choice E) The risk of stroke is increased in patients with diabetes mellitus. However, cerebrovascular accidents account for about 10% of total mortality in patients with type 2 diabetes mellitus versus 40% from coronary heart disease.

Educational objective:
Patients with **noncoronary atherosclerotic disease**, **diabetes mellitus**, or **chronic kidney disease** are at the same risk of cardiovascular events (eg, myocardial infarction, stroke) as patients with known coronary heart disease. Coronary heart disease is the most common cause of death in patients with diabetes mellitus.

Pathology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 45-year-old man comes to the office due to slowly progressive back and joint pain. In particular, his knee and ankle joints are stiff and painful when he walks. Over the past year, the patient has also experienced excessive sweating, and his ring and shoe sizes have increased. He has no prior medical issues and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Physical examination shows coarse facial features with a prominent forehead, protruding jaw, and widely separated maxillary teeth. There is mild swelling and crepitus of the knees and ankles bilaterally. Which of the following is most likely to be associated with this patient's condition?

A. Aortic root dilation
B. Bicuspid aortic valve
C. Left ventricular hypertrophy
D. Mitral valve prolapse
E. Pericardial effusion

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A. Aortic root dilation
B. Bicuspid aortic valve
C. Left ventricular hypertrophy
D. Mitral valve prolapse
E. Pericardial effusion

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A 45-year-old man comes to the office due to slowly progressive back and joint pain. In particular, his knee and ankle joints are stiff and painful when he walks. Over the past year, the patient has also experienced excessive sweating, and his ring and shoe sizes have increased. He has no prior medical issues and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Physical examination shows coarse facial features with a prominent forehead, protruding jaw, and widely separated maxillary teeth. There is mild swelling and crepitus of the knees and ankles bilaterally. Which of the following is most likely to be associated with this patient's condition?

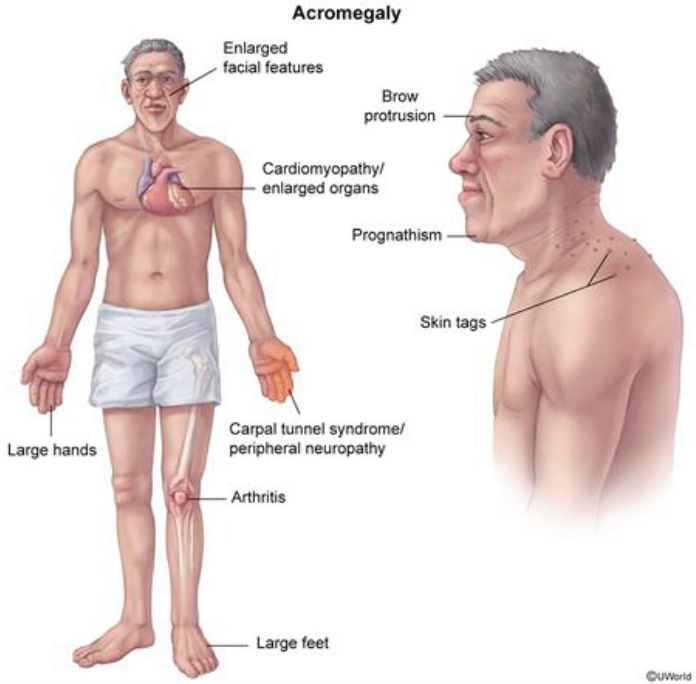
A. Aortic root dilation (18%)
B. Bicuspid aortic valve (3%)
C. Left ventricular hypertrophy (66%)
D. Mitral valve prolapse (10%)
E. Pericardial effusion (2%)

66% 51 secs 02/02/2021

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This patient has bony overgrowth (ie, frontal bossing; enlarged jaw, hands, and feet) consistent with acromegaly. **Acromegaly** is caused by excessive production of **growth hormone** (GH) and is most often due to a pituitary somatotroph adenoma. Excess GH both directly and indirectly (via release of insulin-like growth factor 1 from the liver) leads to overgrowth of many tissues, including bone, cartilage, and visceral organs.

In the heart, chronic GH elevation stimulates cardiac growth, causing **left ventricular hypertrophy**, diastolic dysfunction, and possible heart failure. The joints are also frequently involved in acromegaly, as excessive GH causes hyperplasia of articular chondrocytes and synovial hypertrophy, leading to wear and degeneration of articular cartilage and periarticular bone (hypertrophic **arthropathy**). Soft tissue involvement is also common and manifests as macroglossia, deepening of the voice (due to laryngeal soft tissue growth), carpal tunnel syndrome, and peripheral neuropathy.

(Choices A and D) Marfan syndrome is an inherited condition caused by a defect in fibrillin-1. Cardiovascular complications include cystic medial degeneration of the aorta (with aneurysmal dilation and dissection), aortic regurgitation, and mitral valve prolapse. However, unlike the bony enlargement in acromegaly, the typical marfanoid habitus is characterized by a tall, slender build and an increased ratio of limb length-to-height.

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limb length-to-height.

(Choice B) Ehlers-Danlos syndrome is due to an autosomal recessive defect in lysyl hydroxylase, which leads to defects in connective tissues (eg, fragile, hyperextensible skin). Musculoskeletal manifestations include hypermobile joints, pectus excavatum, and scoliosis. Valvular heart disease is common and can present as bicuspid aortic valve or mitral/tricuspid valve prolapse.

(Choice E) Patients with untreated hypothyroidism can have a pericardial effusion, and also frequently have nonpitting edema (myxedema) due to excessive deposition of mucopolysaccharides and adipogenesis in the dermis and subcutaneous tissues. However, bony enlargement is not characteristic.

Educational objective:

Acromegaly is caused by excessive production of growth hormone, usually due to a pituitary somatotroph adenoma. Musculoskeletal manifestations include bony hypertrophy (eg, frontal bossing; enlarged jaw, hands, and feet) and osteoarthritis. Left ventricular hypertrophy is often common in acromegaly and may progress to heart failure.

References

- GH and the cardiovascular system: an update on a topic at heart.

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A 16-year-old girl is brought to the office by her mother due to concern about excessive weight loss. The patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor seen in the fingers when the arms are outstretched. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

A. Diffuse atrophy of the thyroid follicles with decreased colloid
B. Extensive lymphocytic infiltrate with germinal center formation
C. Inflammatory disruption of the follicles and multinucleated giant cells
D. Small clusters of spindle cells and foci of C-cell hyperplasia
E. Tall columnar follicular epithelium with scalloped margins of the colloid

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patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor seen in the fingers when the arms are outstretched. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

- ✓ A. Diffuse atrophy of the thyroid follicles with decreased colloid (57%)
- B. ~~Extensive lymphocytic infiltrate with germinal center formation~~ (9%)
- C. ~~Inflammatory disruption of the follicles and multinucleated giant cells~~ (4%)
- D. ~~Small clusters of spindle cells and foci of C-cell hyperplasia~~ (2%)
- ✗ E. Tall columnar follicular epithelium with scalloped margins of the colloid (25%)

Incorrect

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This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH are indicative of **thyrotoxicosis**. However, her thyroid is small and serum **thyroglobulin is undetectable**, which suggests an **exogenous source** of thyroid hormone. Thyroglobulin is a glycoprotein produced by thyroid follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the formation of thyroid hormone. A small amount is released by the thyroid in normal function. Low levels, as in this patient, suggest noninflammatory **suppression of thyroid activity**.

In light of her mother's hypothyroidism, which suggests a possible source of levothyroxine tablets, this patient is likely surreptitiously taking thyroid hormone in an attempt to lose weight. Exogenous thyrotoxicosis can also occur in patients taking over-the-counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation suppresses TSH, which decreases iodine organification and colloid formation resulting in **atrophy of thyroid follicles**.

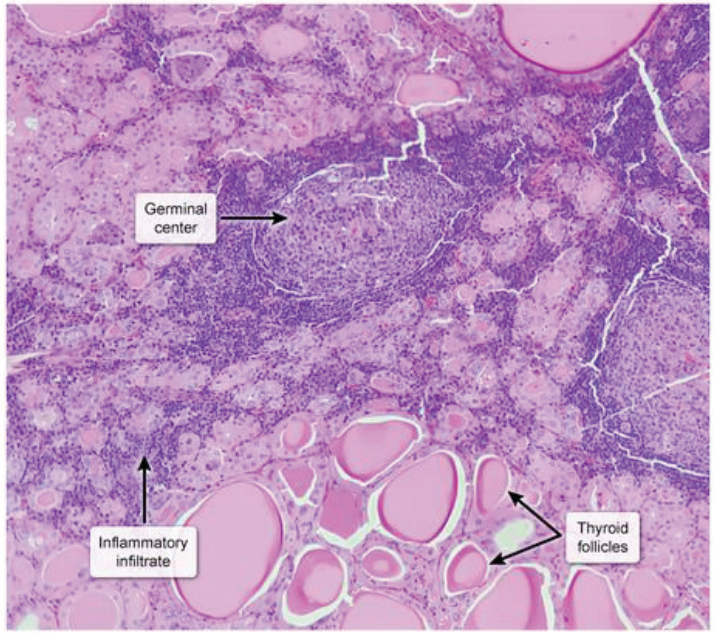
(Choice B) Histopathology in chronic autoimmune (Hashimoto) thyroiditis is characterized by a mononuclear infiltrate consisting of lymphocytes and plasma cells, often with germinal centers. Hashimoto thyroiditis typically presents with primary hypothyroidism (elevated TSH, low free T4) and goiter; although Hashimoto's can occasionally present with an initial hyperthyroid phase, these patients will have elevated

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Hashimoto thyroiditis



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Hashimoto's can occasionally present with an initial hyperthyroid phase, these patients will have elevated

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(Choice C) Subacute granulomatous (de Quervain) thyroiditis is characterized by disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. Patients may have hyperthyroidism but typically have a painful, tender thyroid gland and high levels of thyroglobulin due to destructive thyroiditis.

(Choice D) Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting parafollicular C cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits (derived from calcitonin). Clinical features include diarrhea, flushing, and thyroid nodules, but TSH and free T4 are normal.

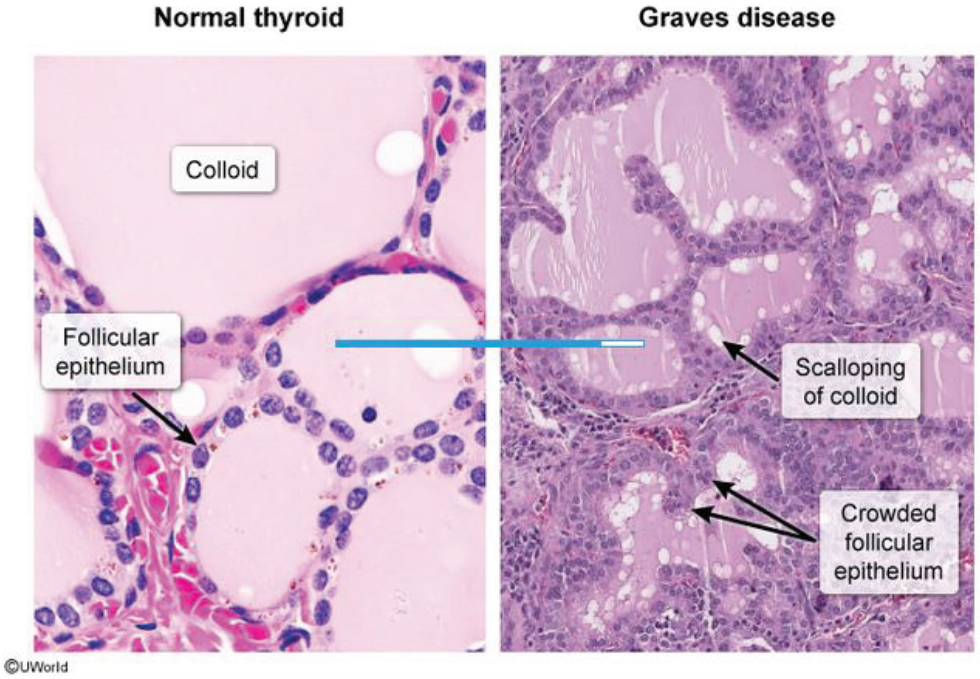
(Choice E) Graves disease presents with a diffusely enlarged thyroid gland associated with hyperthyroidism, exophthalmos, and pretibial myxedema. The thyroid follicular epithelium is tall and crowded with hyperactive reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin would be seen due to increased thyroid metabolic activity.

Educational objective:
Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and low/undetectable thyroglobulin. It can occur with surreptitious levothyroxine abuse, use of animal-sourced thyroid supplements, and erroneous dosing of thyroid replacement therapy. Over time, the lack of TSH stimulation causes the thyroid follicles to become atrophic.

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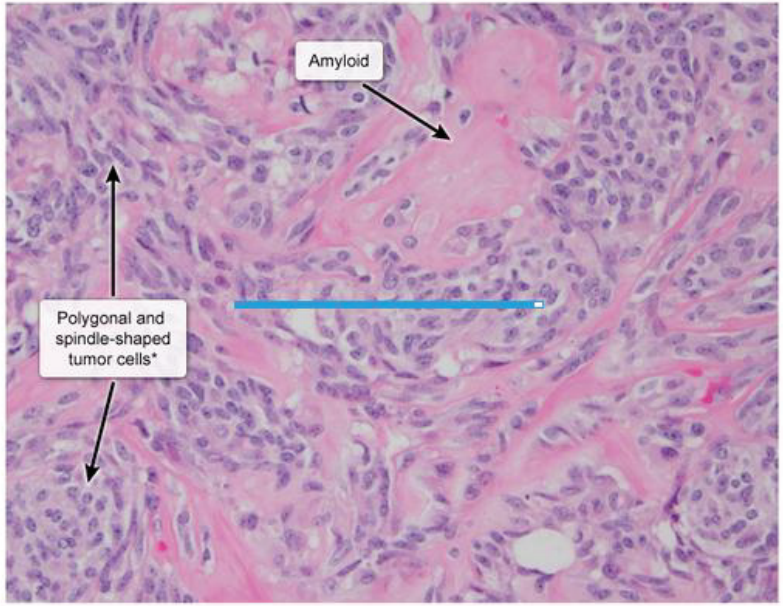
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Medullary thyroid carcinoma



*Derived from C (parafollicular) cells

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A 30-year-old woman comes to the office due to excessive weight gain without any changes in her diet or physical activity. She has also been feeling more tired lately and has had frequent constipation. The patient has no prior medical problems and takes no medications. She has been pregnant once and gave birth to a healthy infant 3 years ago. Family history is significant for a thyroid disorder in her mother. Blood pressure is 116/90 mm Hg and pulse is 58/min. BMI is 28.5 kg/m^2. Physical examination reveals a diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
A.	Increased	Decreased	Normal
B.	Increased	Normal	Normal
C.	Increased	Increased	Increased
D.	Normal	Normal	Decreased

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birth to a healthy infant 3 years ago. Family history is significant for a thyroid disorder in her mother. Blood pressure is 116/90 mm Hg and pulse is 58/min. BMI is 28.5 kg/m^2. Physical examination reveals a diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)
A.	Increased	Decreased	Normal
B.	Increased	Normal	Normal
C.	Increased	Increased	Increased
D.	Normal	Normal	Decreased
E.	Decreased	Increased	Increased
F.	Decreased	Normal	Normal

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diffusely enlarged and nontender thyroid with no nodules. There is delayed relaxation of deep tendon reflexes. Her hair is thin and the skin appears dry. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	TSH	Thyroxine (T4)	Triiodothyronine (T3)	
✓ A.	Increased	Decreased	Normal	(83%)
B.	~~Increased~~	~~Normal~~	~~Normal~~	(2%)
C.	~~Increased~~	~~Increased~~	~~Increased~~	(1%)
D.	~~Normal~~	~~Normal~~	~~Decreased~~	(8%)
E.	~~Decreased~~	~~Increased~~	~~Increased~~	(2%)
F.	~~Decreased~~	~~Normal~~	~~Normal~~	(0%)

Correct

83%
Answered correctly

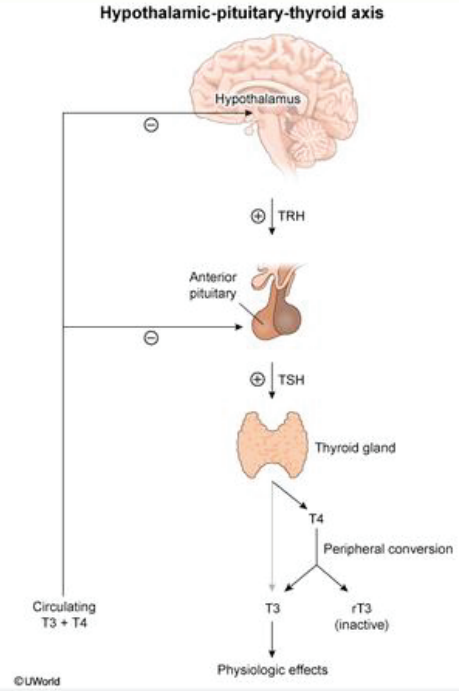
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Regulation of thyroid hormone secretion involves feedback inhibition along the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which triggers release of TSH from the pituitary. TSH stimulates secretion of thyroid hormone from the thyroid, which in turn inhibits release of both TRH and TSH. Thyroid hormone exists in 2 primary forms: T4 (thyroxine), the predominant form secreted by the thyroid, and T3 (triiodothyronine), the more active form produced mainly by deiodination of T4 in peripheral tissues.

This patient has a very typical presentation of **primary hypothyroidism** with weight gain, fatigue, and a delayed relaxation phase of deep tendon reflexes. Her diffuse goiter suggests chronic autoimmune (Hashimoto) thyroiditis, which is the most common cause of hypothyroidism in developed countries. As autoimmune destruction of the gland progresses, thyroid hormone production declines, leading to loss of feedback inhibition of TSH secretion; therefore, patients have **low T4** and **elevated TSH** levels. However, because T3 is produced mainly in peripheral tissues and has a short half-life, serum T3 levels fluctuate widely and correlate poorly with clinical status; **T3 is often normal** in primary hypothyroidism.

(Choice B) TSH secretion is very sensitive to changes in thyroid status and rises in response to even small declines in thyroid hormone production. Subclinical hypothyroidism is a common biochemical state in which an elevated TSH is necessary to maintain normal thyroid hormone levels. However, most patients

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(Choice B) TSH secretion is very sensitive to changes in thyroid status and rises in response to even small declines in thyroid hormone production. Subclinical hypothyroidism is a common biochemical state in which an elevated TSH is necessary to maintain normal thyroid hormone levels. However, most patients are asymptomatic.

(Choices C, E, and F) Primary hyperthyroidism (eg, Graves disease) is characterized by elevated thyroid hormone levels and suppressed TSH. Subclinical hyperthyroidism is characterized by suppressed TSH with normal thyroid hormone levels. Central (secondary) hyperthyroidism (eg, TSH-secreting pituitary adenoma) shows elevated levels of both TSH and thyroid hormone. Common clinical features of hyperthyroidism (primary or secondary) include weight loss, heat intolerance, and tachycardia; patients with subclinical hyperthyroidism may be asymptomatic or have mild symptoms. T3 levels correlate with clinical status in hyperthyroidism more closely than in hypothyroidism and are often elevated.

(Choice D) Euthyroid sick syndrome is a constellation of abnormal thyroid tests seen in patients with severe systemic illness (eg, sepsis). Excess cortisol, inflammatory cytokines, starvation, and certain medications (eg, amiodarone) can cause reduced conversion of T4 to T3, leading to low serum T3; reverse T3 (the inactive metabolite of T4) is typically elevated but TSH and T4 are usually normal.

Educational objective:

Primary hypothyroidism is characterized by decreased T4 levels and increased TSH. T3 is primarily

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hyperthyroidism (primary or secondary) include weight loss, heat intolerance, and tachycardia; patients with subclinical hyperthyroidism may be asymptomatic or have mild symptoms. T3 levels correlate with clinical status in hyperthyroidism more closely than in hypothyroidism and are often elevated.

(Choice D) Euthyroid sick syndrome is a constellation of abnormal thyroid tests seen in patients with severe systemic illness (eg, sepsis). Excess cortisol, inflammatory cytokines, starvation, and certain medications (eg, amiodarone) can cause reduced conversion of T4 to T3, leading to low serum T3; reverse T3 (the inactive metabolite of T4) is typically elevated but TSH and T4 are usually normal.

Educational objective:

Primary hypothyroidism is characterized by decreased T4 levels and increased TSH. T3 is primarily produced by conversion from T4 in peripheral tissues; serum levels widely fluctuate due to its short half life, and can often be within the normal range in patients with hypothyroidism.

References

- Pitfalls in the measurement and interpretation of thyroid function tests

Physiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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A 20-year-old woman is brought to the emergency department due to intractable vomiting and abdominal pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

A. Ceftriaxone
B. Dexamethasone
C. Dopamine
D. Epinephrine
E. Levothyroxine

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pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

A. Ceftriaxone (3%)
B. Dexamethasone (56%)
C. Dopamine (4%)
D. Epinephrine (18%)
E. Levothyroxine (15%)

56%
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Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Illness/injury/surgery in patient with chronic AI • Pituitary apoplexy
Clinical features	• **Hypotension** & **shock** • Nausea, vomiting, abdominal pain • Fever, generalized weakness
Treatment	• **Hydrocortisone** or **dexamethasone** • Rapid intravenous volume repletion

AI = adrenal insufficiency.

This patient most likely has acute **adrenal crisis**. Her history of hypothyroidism puts her at increased risk for other autoimmune endocrinopathies (eg, autoimmune adrenalitis), and her weight loss and hyperpigmentation are suggestive of chronic **primary adrenal insufficiency** (Addison disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase

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This patient most likely has acute **adrenal crisis**. Her history of hypothyroidism puts her at increased risk for other autoimmune endocrinopathies (eg, autoimmune adrenalitis), and her weight loss and hyperpigmentation are suggestive of chronic **primary adrenal insufficiency** (Addison disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase in glucocorticoid production, but patients with adrenal insufficiency cannot mount such a response.

Adrenal crisis is characterized by **severe hypotension** and refractory shock. Associated symptoms include abdominal pain, vomiting, weakness, and fever. In addition to aggressive **fluid resuscitation**, treatment of adrenal crisis requires immediate **glucocorticoid supplementation** with hydrocortisone or dexamethasone. Treatment should begin immediately without waiting for results of diagnostic studies, and the response is usually rapid.

(Choice A) Antibiotics may be necessary if evidence of infection is found. However, treatment with glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However,

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glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However, hypotension in adrenal crisis is often refractory to vasopressors because glucocorticoids have a permissive effect on vasoconstriction.

(Choice E) Clinical features of hypothyroid crisis may include hypoglycemia and hypotension, as seen in this patient, but would usually also include altered sensorium, hypothermia, bradycardia, and hypoventilation. In addition, due to the long plasma half life of levothyroxine, missing 2 days of therapy would be unlikely to cause a symptomatic drop in thyroid hormone levels.

Educational objective:

Patients with adrenal insufficiency are not able to increase glucocorticoid production in response to acute stress (eg, illness, surgery). Adrenal crisis is characterized by severe hypotension, abdominal pain, vomiting, weakness, and fever. In addition to aggressive fluid resuscitation, treatment requires immediate glucocorticoid supplementation.

References

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A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy cells, this sugar alcohol is normally metabolized into which of the following substances to facilitate excretion?

- A. Fructose
- B. Galactitol
- C. Galactose
- D. Glucose
- E. Xylulose

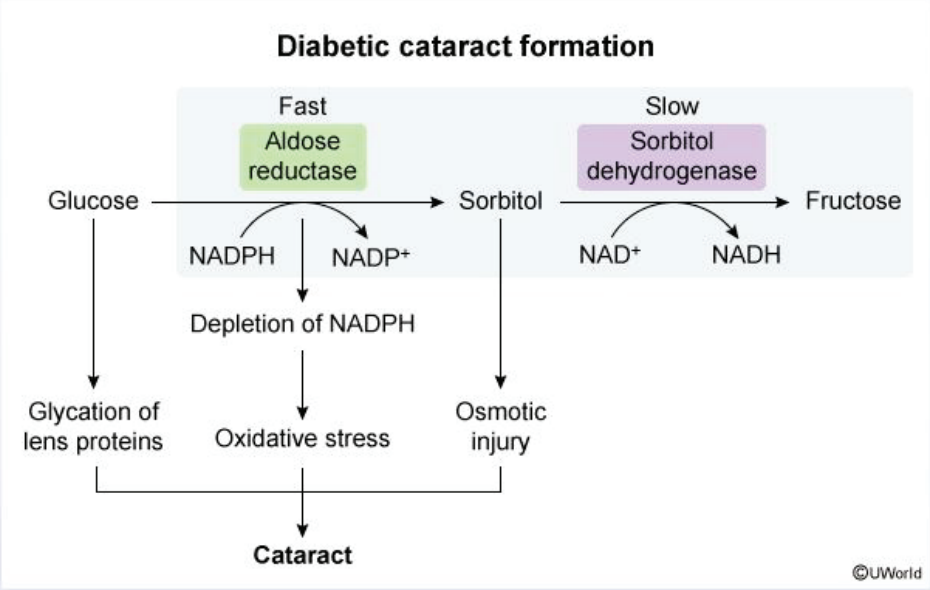
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- A. Fructose (62%)
- B. Galactitol (16%)
- C. Galactose (6%)
- D. Glucose (8%)
- E. Xylulose (6%)

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This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the red reflex with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight exposure, **diabetes mellitus**, and glucocorticoid use. In this patient, long-term hyperglycemia most likely contributed to cataract

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This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the red reflex with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight exposure, **diabetes mellitus**, and glucocorticoid use. In this patient, long-term hyperglycemia most likely contributed to cataract formation by causing **oversaturation of the polyol pathway**.

The first step in the polyol pathway (an alternative route of glucose metabolism) is the conversion of glucose into sorbitol by aldose reductase. Sorbitol cannot readily cross cell membranes and is therefore trapped inside the cells where it forms. The second enzyme in the pathway, sorbitol dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina, lens, kidney, and peripheral nerves.

Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

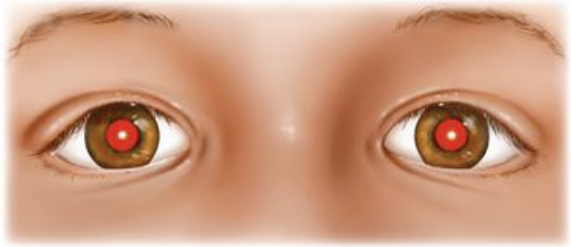
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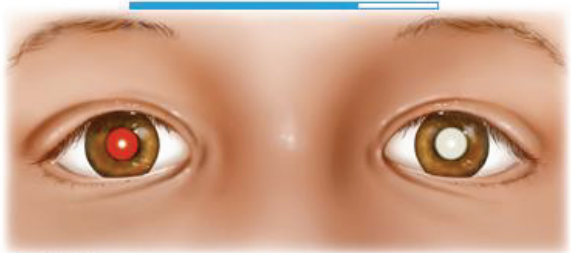
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Normal eyes & white reflex



Normal eyes
Red reflexes & corneal light reflexes are equal.



Absent reflex
White reflex on abnormal eye can result from opacities of the lens (eg, cataract) or tumor (eg, retinoblastoma).

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leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted by the cells and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase. Chronic hyperglycemia overwhelms this pathway, causing intracellular sorbitol accumulation and increased osmotic/oxidative stress. This accelerates cataract development in patients with diabetes, and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy.

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A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) weight loss. The patient has type 1 diabetes mellitus and has noticed decreased insulin requirements over this time. She has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Physical examination shows a generalized increase in pigmentation of the skin, especially involving the palmar creases. Measurement of serum cortisol before and after administration of exogenous adrenocorticotropic hormone (ACTH) shows no difference in the levels. Which of the following changes in serum laboratory values is most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate
A.	Normal	↓	↓	↑
B.	↓	↑	↑	↓
C.	↓	↓	↓	↑
D.	Normal	↑	Normal	Normal
E.	Normal	↓	↑	↓

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	Sodium	Potassium	Chloride	Bicarbonate	
A.	~~Normal~~	↓	↓	↑	(16%)
✓ B.	↓	↑	↑	↓	(51%)
C.	↓	↓	↓	↑	(7%)
D.	Normal	↑	Normal	Normal	(13%)
E.	~~Normal~~	↓	↑	↓	(10%)

Correct

51%

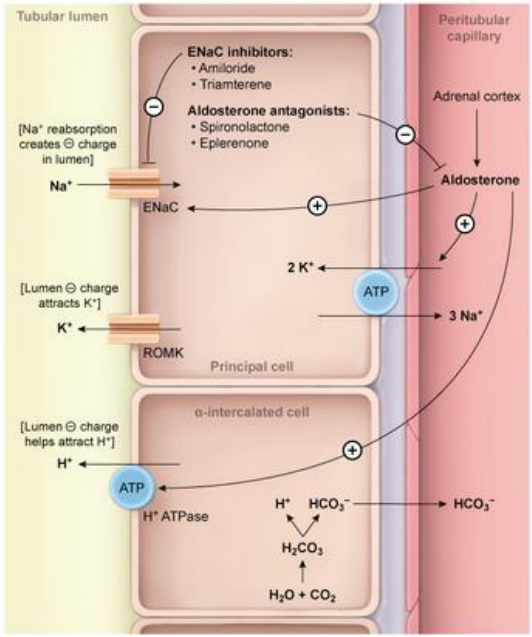
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Action of aldosterone in the collecting duct of the nephron



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This patient's fatigue and weight loss are likely due to **primary adrenal insufficiency** (Addison disease). Type 1 diabetes mellitus is caused by autoimmune destruction of pancreatic beta cells and is associated with an increased risk of other autoimmune endocrinopathies. Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency and results from autoantibodies against all 3 zones of the adrenal cortex. Because the main defect is in the adrenal gland, **exogenous ACTH** administration **does not increase cortisol** levels. Decreased negative feedback of cortisol on the pituitary gland increases release of ACTH and melanocyte-stimulating hormone, resulting in **hyperpigmentation**. Patients with diabetes often have reduced insulin requirements due to decreased appetite, weight loss, and increased insulin sensitivity (glucocorticoids decrease insulin sensitivity).

Hypoaldosteronism in primary adrenal insufficiency leads to decreased Na^+ reabsorption and decreased urinary excretion of K^+ and H^+. Decreased H^+ excretion causes a nonanion gap metabolic acidosis with low plasma HCO_3^-. This leads to compensatory Cl^- retention to maintain electrical neutrality of the extracellular fluid. The hypotension induced by lack of aldosterone stimulates vasopressin release, increasing free water reabsorption and further exacerbating hyponatremia. As a result, patients with primary adrenal insufficiency present with **hyponatremia**, **hyperkalemia**, hyperchloremia, and **nonanion gap metabolic acidosis**.

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acidosis.

(Choice A) Mineralocorticoid excess (ie, primary hyperaldosteronism) leads to Na^+ retention, urinary loss of K^+ and H^+, and metabolic alkalosis (ie, increased plasma HCO_3^-). However, significant hypernatremia is avoided due to aldosterone escape.

(Choice C) Thiazide diuretics block Na^+/Cl^- reabsorption in the distal tubule. This allows more Na^+ to reach the collecting tubule, enhancing K^+ and H^+ excretion. Findings include hyponatremia, hypokalemia, and metabolic alkalosis.

(Choice D) Isolated hyperkalemia is usually due to excess dietary potassium intake or cell lysis (eg, hemolysis, rhabdomyolysis). Hyperkalemia can also be caused by decreased shift of K^+ into the cells due to insulin deficiency or occasionally by beta 2 antagonists (eg, metoprolol).

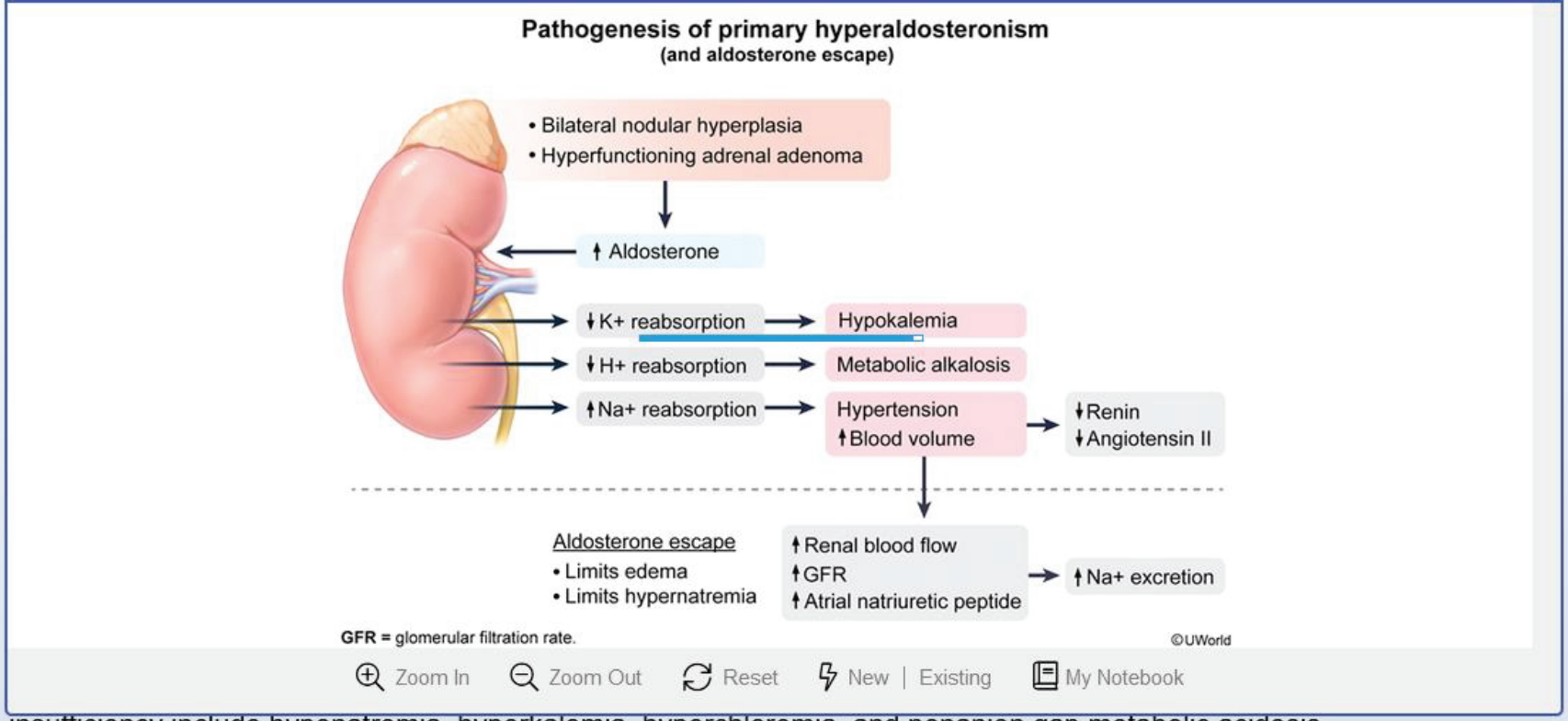
(Choice E) Normal serum sodium in the setting of hypokalemia and hyperchloremic metabolic acidosis suggests distal hypokalemic or proximal renal tubular acidosis.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk for other autoimmune endocrinopathies, including primary adrenal insufficiency (Addison disease). Electrolyte abnormalities in primary adrenal insufficiency include hyponatremia, hyperkalemia, hyperchloremia, and nonanion gap metabolic acidosis

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acidosis.

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References

- Diagnosis and classification of Addison's disease (autoimmune adrenalitis).

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A patient is treated with a gonadotropin-releasing hormone (GnRH) infusion. An intravenous line is placed and connected to a reservoir through a computerized pump. The pump is programmed to deliver a predetermined dose of GnRH every 90 minutes, which results in a sharp rise in serum GnRH levels with each dose, followed by a rapid return to baseline. LH and FSH levels are monitored in the initial phase of treatment. Which of the following is the most likely indication for using this GnRH infusion?

A. Breast cancer
B. Endometriosis
C. Infertility
D. Precocious puberty
E. Prostate cancer

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- A. Breast cancer (0%)
- B. Endometriosis (1%)
- ✓ C. Infertility (87%)
- D. Precocious puberty (4%)
- E. Prostate cancer (4%)

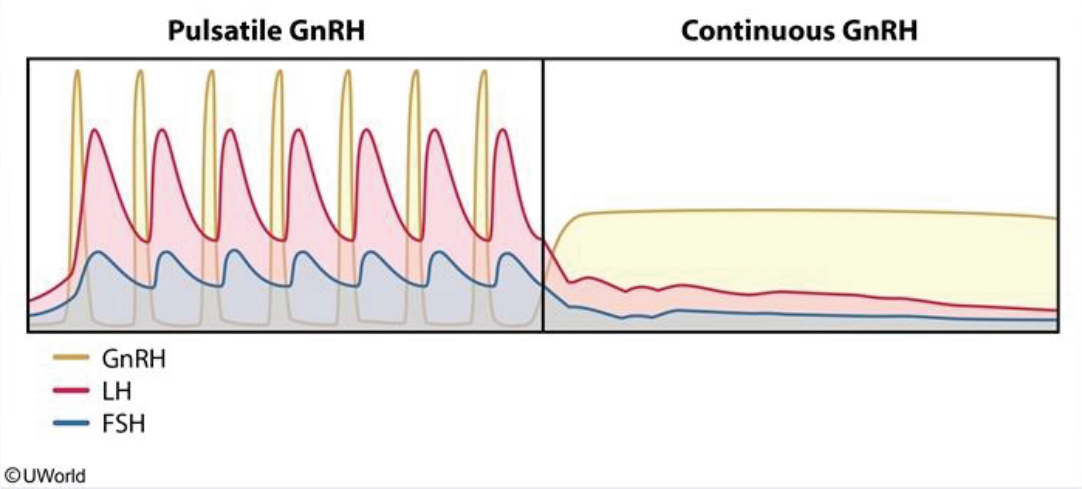
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87%
Answered correctly

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Gonadotropin-releasing hormone (GnRH) is a polypeptide that is normally released from the anterior hypothalamus in a pulsatile manner. GnRH is carried to the anterior pituitary via the portal circulation, where it stimulates FSH and LH production. **Pulsatile** stimulation of pituitary gonadotrophin cells by GnRH leads to upregulation of GnRH receptors and enhanced FSH and LH secretion. FSH and LH are responsible for development of the dominant follicle in the ovaries. Optimal frequency and amplitude of GnRH pulses are crucial for FSH and LH release and subsequent ovulation.

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GnRH pulses are crucial for FSH and LH release and subsequent ovulation.

Anovulation due to hypogonadotropic hypogonadism is a common form of **infertility** that can be treated by pulsatile administration of GnRH. GnRH has a very short half-life and is given by a programmable pump that delivers a predetermined dose at physiologic intervals. Ovulation occurs in most patients in 10-20 days. Signs of ovulation include loss of a dominant follicle on ultrasound, surge in urine LH levels, rise in serum progesterone levels, and rise in basal body temperature.

(Choices A, B, D, and E) Constant, rather than pulsatile, GnRH activity causes down-regulation of the GnRH receptors on pituitary gonadotrophin cells, which suppresses LH and FSH secretion. Although it is possible to use a pump to administer GnRH at a steady rate, it has a very short half-life, and long-acting GnRH analogs (eg, leuprolide) are easier to use and can be given monthly by intramuscular injection. Long-acting GnRH analog therapy is used when suppression of gonadal function is desired, such as in certain patients with prostate cancer, endometriosis, precocious puberty, or premenopausal breast cancer.

Educational objective:
Pulsatile administration of gonadotropin-releasing hormone (GnRH) stimulates FSH and LH release and is useful for the treatment of infertility. Nonpulsatile (constant) infusion of GnRH, or a long-acting analog, suppresses FSH and LH release and subsequently suppresses gonadal function.

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A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

A. Ascorbic acid
B. Carnitine
C. Pyridoxine
D. Thiamine
E. Tyrosine
F. Vitamin K

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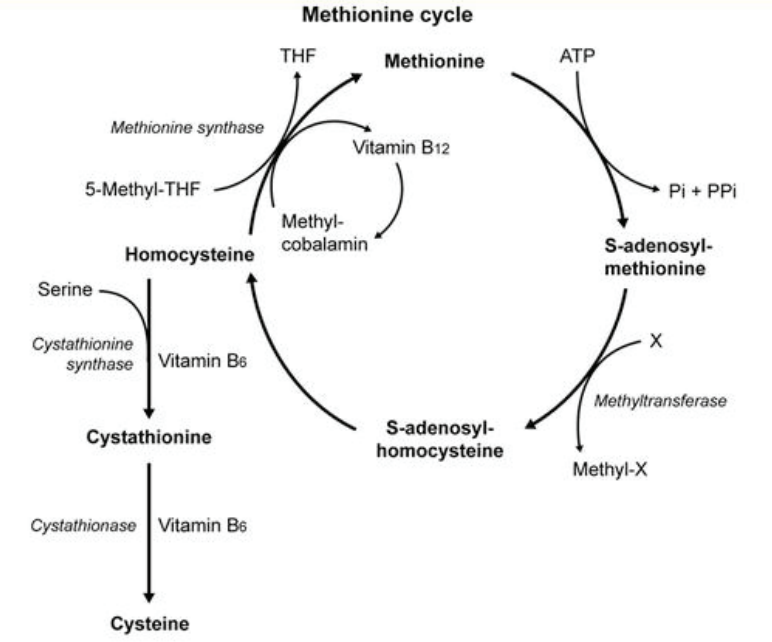
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A. ~~Ascorbic acid~~ (31%)
B. ~~Carnitine~~ (7%)
✓ C. Pyridoxine (39%)
D. Thiamine (5%)
E. ~~Tyrosine~~ (6%)
F. ~~Vitamin K~~ (9%)

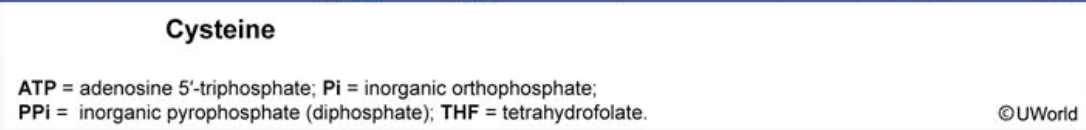
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This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intellectual disability**. Other clinical manifestations include a Marfanoid habitus (eg, elongated limbs, arachnodactyly, scoliosis). Patients are at high risk for **thromboembolic occlusion** of both large and small vessels, especially those of the brain, heart, and kidneys. Thromboembolic complications are the major cause of morbidity and mortality in these patients.

Homocystinuria is most frequently caused by an **autosomal recessive** deficiency of cystathionine beta-synthase, an enzyme that requires **pyridoxine (vitamin B6)** as a cofactor. Approximately 50% of affected patients respond to high doses of pyridoxine, which improves residual enzymatic activity and reduces plasma homocysteine levels. Additional treatment includes dietary **restriction of methionine**.

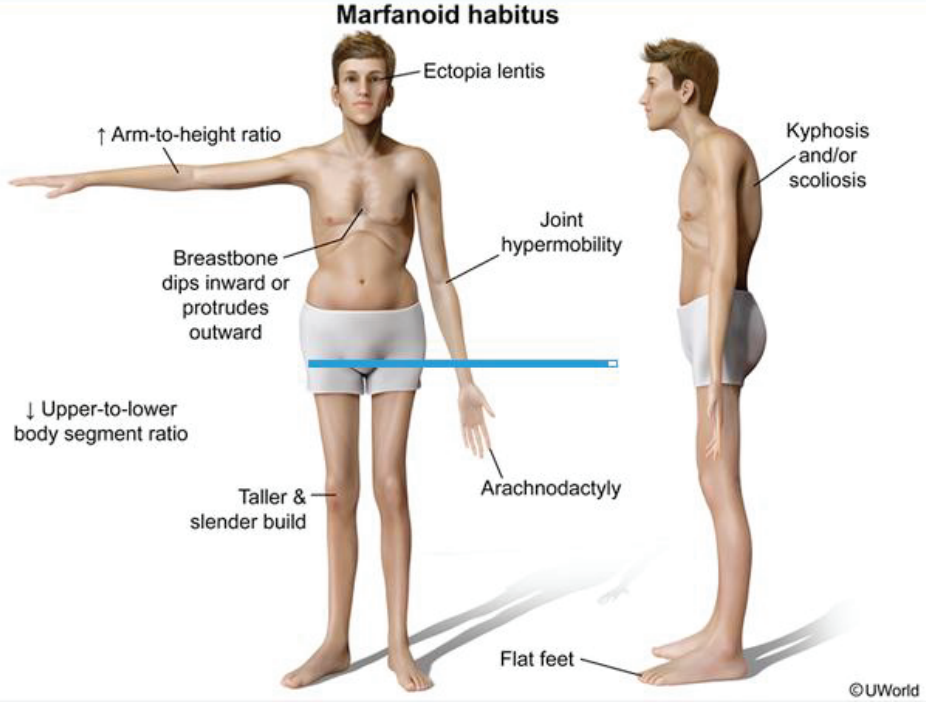
(Choice A) Vitamin C is a necessary cofactor for the hydroxylation of proline and lysine residues in collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes scurvy.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in

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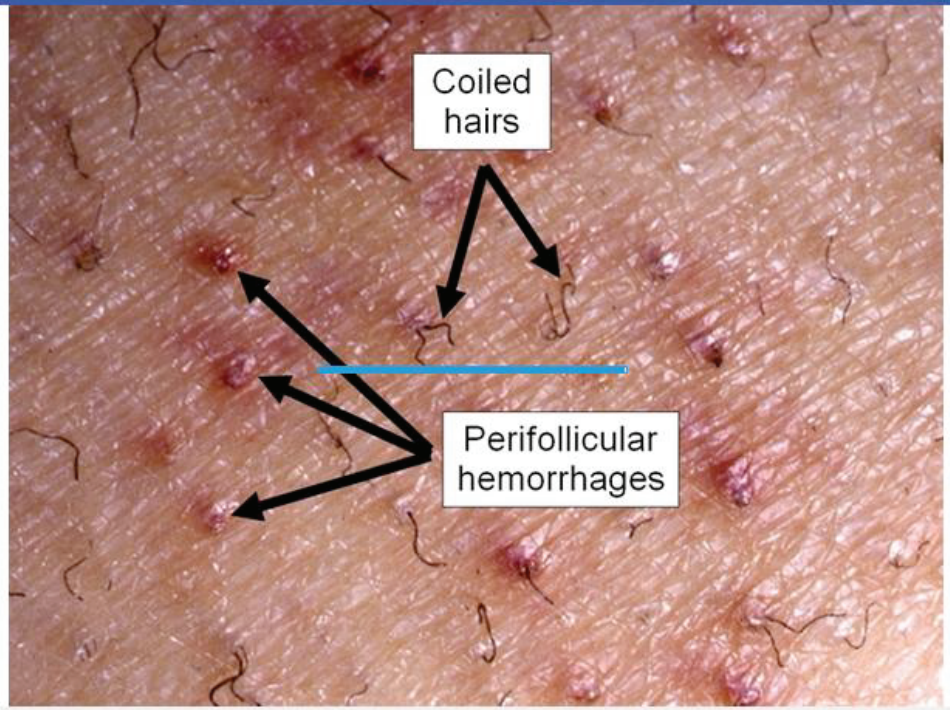


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collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes scurvy.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in carnitine (eg, primary systemic carnitine deficiency) lead to fatty acid oxidation defects in cardiac and skeletal muscle.

(Choice D) Thiamine (vitamin B1) deficiency can cause dry and wet beriberi and Wernicke-Korsakoff syndrome.

(Choice E) Tyrosine is a nonessential amino acid and the precursor for catecholamines such as dopamine, epinephrine, and norepinephrine.

(Choice F) Vitamin K is involved in the post-translational conversion of glutamate to gamma-carboxyglutamic acid. This modification is necessary for the function of many clotting factors and regulatory proteins involved in the coagulation cascade.

Educational objective:
Homocystinuria is most commonly caused by cystathionine synthase deficiency. Affected individuals have marfanoid habitus, ectopia lentis, and developmental delay. Significant morbidity and mortality are due primarily to thromboembolism. Many patients with homocystinuria respond dramatically to pyridoxine (vitamin B6) supplementation.

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A 21-year-old man comes to the office due to recent weight loss and fatigue. The patient is a college athlete and states, "My coach wants me to put on more weight, but I can't seem to do it. It doesn't matter how much I eat, I keep losing weight. I've been really thirsty and drinking lots of water lately too, and it's causing me to use the bathroom frequently during practice. I'm worried that I'm going to get dropped from the team if I don't get myself together." He is sexually active and has 1 lifetime partner. The patient's father was diagnosed with colon cancer at age 64. Which of the following studies would be the best next step to establish the diagnosis in this patient?

- A. Colonoscopy
- B. Hemoglobin A1c
- C. HIV testing
- D. Serum TSH level
- E. Urinalysis
- F. Urine drug screen

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- A. Colonoscopy (1%)
- ✓ B. Hemoglobin A1c (62%)
- C. HIV testing (0%)
- D. Serum TSH level (12%)
- E. Urinalysis (19%)
- F. Urine drug screen (2%)

Correct

62%

53 secs

10/05/2020

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Type 1 diabetes mellitus	
Etiology	• Autoimmune destruction of pancreatic beta cells • **Insulin deficiency**
Signs & symptoms	• Polydipsia, polyuria • Polyphagia • Weight loss • Blurred vision • Ketoacidosis
Diagnosis	• **Fasting glucose** (≥126 mg/dL) • **Hemoglobin A1c** (≥6.5%) • Random glucose (≥200 mg/dL) • Oral glucose tolerance test

This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal

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This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

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(Choice C) Acute HIV presents as an acute viral syndrome with nonspecific symptoms and signs (eg, weight loss, fatigue). However, polyuria and polydipsia suggest diabetes rather than acute HIV.

(Choice D) It is possible that weight loss and polyuria are due to thyrotoxicosis, but the absence of other symptoms of thyroid disease (eg, palpitations, heat intolerance, excessive sweating) makes this less likely.

(Choice E) Acute cystitis can cause frequent urination but the total urine volume is not increased, and polydipsia and weight loss are more suggestive of diabetes mellitus. Although urinalysis can detect glucosuria, it has low sensitivity for diabetes and should not be used to confirm the diagnosis.

(Choice F) Although surreptitious drug abuse can be considered in patients with weight loss or other unexplained symptoms, a hemoglobin A1c test is more likely to be diagnostic in light of this patient's polyuria and polydipsia.

Educational objective:
Type 1 diabetes mellitus typically presents subacutely with polyuria and polydipsia accompanied by fatigue and weight loss. The diagnosis can be confirmed with a fasting blood glucose or hemoglobin A1c measurement.

References

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A 42-year-old woman with Graves disease is hospitalized for elective total thyroidectomy. Her hyperthyroid symptoms have been controlled with methimazole and propranolol, but she still has a goiter. The patient has no other medical problems. She undergoes total thyroidectomy without any immediate operative complications and feels well the next day. Laboratory results are as follows:

Serum chemistry

Sodium	141 mEq/L
Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

A. Alendronate

B. Calcitriol

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Sodium	141 mEq/L
Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

A. Alendronate
B. Calcitriol
C. Cinacalcet
D. Prednisone
E. Radioactive iodine
F. Sevelamer

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Potassium	4.4 mEq/L
Creatinine	0.8 mg/dL
Calcium	7.5 mg/dL

Preoperative electrolyte values were within normal limits. Which of the following medications should be started in this patient?

- A. ~~Alendronate~~ (5%)
- ✓ B. Calcitriol (66%)
- C. Cinacalcet (19%)
- D. ~~Prednisone~~ (1%)
- E. ~~Radioactive iodine~~ (2%)
- F. Sevelamer (3%)

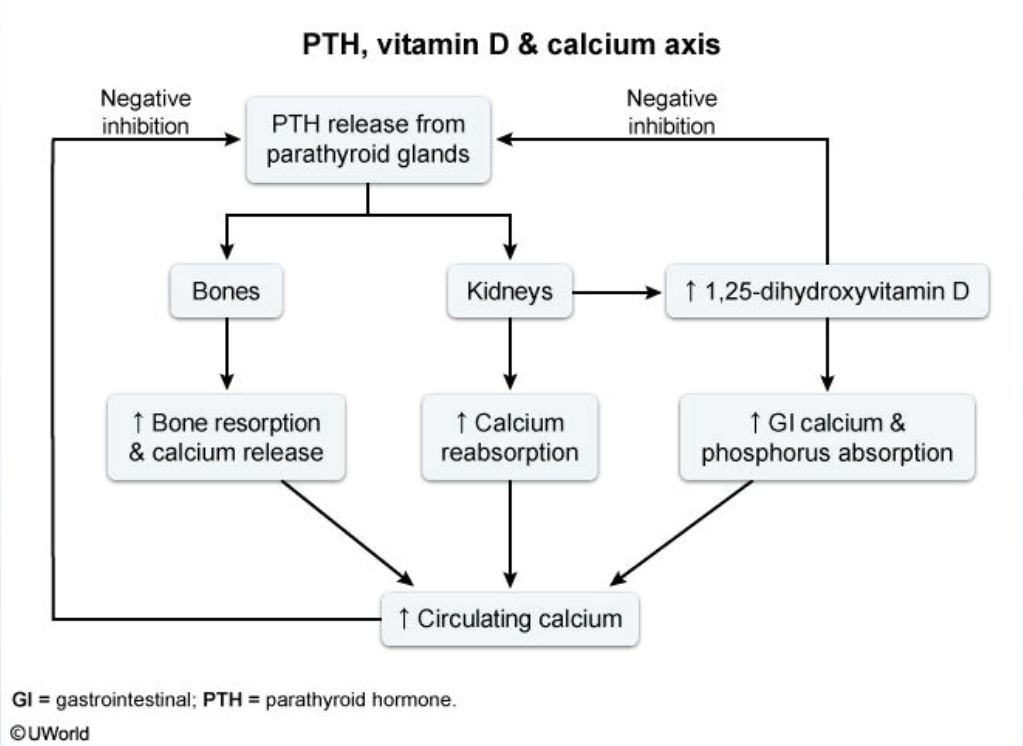
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66%

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09/03/2020

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The **parathyroid glands** are relatively small and indistinct and can be **injured during thyroid surgery** due

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GI = gastrointestinal; **PTH** = parathyroid hormone.

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The **parathyroid glands** are relatively small and indistinct and can be **injured during thyroid surgery** due to direct trauma, devascularization, or inadvertent removal. Transient or permanent postoperative **hypoparathyroidism** can occur following thyroidectomy and cause clinically significant **hypocalcemia**. Patients may be asymptomatic initially but can develop paresthesias (of the lips, mouth, hands, and feet), muscle twitching, or cramps. Worsening hypocalcemia can lead to trismus or tetany with changes in mental status and generalized seizures.

Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia. **Calcitriol**, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and patients with hypoparathyroidism can have inadequate production of calcitriol.

(Choice A) Alendronate is a bisphosphonate that inhibits osteoclast function. Bisphosphonates can worsen hypocalcemia by decreasing the release of calcium from bone.

(Choice C) Cinacalcet is a calcimimetic that allosterically activates the calcium-sensing receptor in the parathyroid gland, decreasing parathyroid hormone release. Cinacalcet is normally used for secondary hyperparathyroidism in patients on dialysis.

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hyperparathyroidism in patients on dialysis.

(Choice D) Glucocorticoids (eg, prednisone) can worsen hypocalcemia by decreasing expression of the vitamin D receptor.

(Choice E) The primary treatment modalities for Graves disease include antithyroid drugs (eg, methimazole), thyroidectomy, and radioiodine ablation. This patient has undergone definitive treatment with thyroidectomy and has no indication for radioiodine therapy.

(Choice F) Sevelamer is a nonabsorbable phosphate-binding polymer that decreases absorption of phosphate in the gastrointestinal tract, and is used to treat hyperphosphatemia in patients on dialysis. Calcium-based phosphate binders (eg, calcium carbonate, calcium acetate) frequently raise calcium levels, but sevelamer has a lesser effect on calcium and would not be adequate treatment for hypocalcemia.

Educational objective:

Postoperative hypoparathyroidism with resultant hypocalcemia is a common complication of thyroidectomy due to inadvertent injury or removal of the parathyroid glands. Postoperative supplementation with oral calcium and vitamin D can be used to treat and prevent postoperative hypocalcemia.

References

- Role of postoperative vitamin D and/or calcium routine supplementation in preventing hypocalcemia

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A 50-year-old man comes to the office following transsphenoidal resection of a growth hormone–secreting pituitary adenoma. Three months ago, the patient was diagnosed with acromegaly. MRI of the pituitary showed a 14-mm sellar mass pressing on the optic chiasm and extending into the right cavernous sinus. The surgeon was able to only partially resect the pituitary mass because of the extension into the right cavernous sinus. Medical therapy for acromegaly with octreotide is planned. Which of the following changes are likely to occur following octreotide treatment in this patient?

	Adenoma size	Growth hormone level	Insulin-like growth factor-1 level
A.	↓	↓	↓
B.	↑	↑	↓
C.	↑	↑	↑
D.	No change	↑	↓
E.	↑	↓	↓

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pituitary adenoma. Three months ago, the patient was diagnosed with acromegaly. MRI of the pituitary showed a 14-mm sellar mass pressing on the optic chiasm and extending into the right cavernous sinus. The surgeon was able to only partially resect the pituitary mass because of the extension into the right cavernous sinus. Medical therapy for acromegaly with octreotide is planned. Which of the following changes are likely to occur following octreotide treatment in this patient?

	Adenoma size	Growth hormone level	Insulin-like growth factor-1 level	
A.	↓	↓	↓	(80%)
B.	↕	↕	↕	(3%)
C.	↕	↕	↕	(1%)
D.	~~No change~~	↕	↕	(7%)
E.	↑	↓	↓	(7%)

Correct

80%

45 secs

11/15/2020

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pituitary adenoma. Three months ago, the patient was diagnosed with acromegaly. MRI of the pituitary showed a 14-mm sellar mass pressing on the optic chiasm and extending into the right cavernous sinus. The surgeon was able to only partially resect the pituitary mass because of the extension into the right cavernous sinus. Medical therapy for acromegaly with octreotide is planned. Which of the following changes are likely to occur following octreotide treatment in this patient?

	Adenoma size	Growth hormone level	Insulin-like growth factor-1 level	
✓ A.	↓	↓	↓	(80%)
B.	↕	↕	↕	(3%)
C.	↕	↕	↕	(1%)
D.	~~No change~~	↕	↕	(7%)
E.	↑	↓	↓	(7%)

Correct

80%

45 secs

11/15/2020

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Acromegaly is characterized by the **excessive secretion of growth hormone** (GH), usually due to a somatotroph **pituitary adenoma**. The actions of GH are mediated primarily by **insulin-like growth factor-1** (IGF-1) from the liver; classic manifestations include bony enlargement of the hands and skull (eg, frontal bossing, jaw malocclusion), arthropathy, cardiomyopathy, and skin thickening. In most cases, initial treatment includes transsphenoidal resection of the tumor. However, if the tumor is unresectable or incompletely resected, the phenotypic manifestations may progress. For these patients, additional medical therapy is indicated.

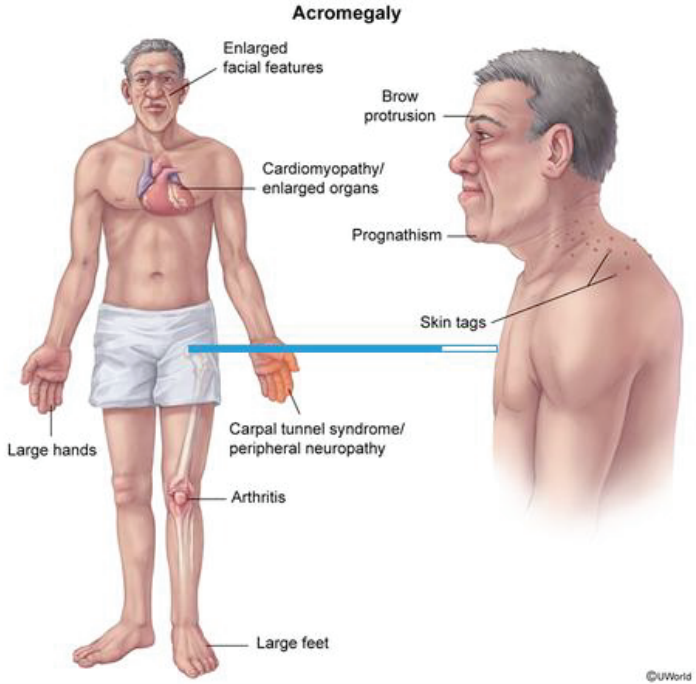
Octreotide is a long-acting octapeptide **somatostatin analogue** that has an altered amino acid sequence in the non–receptor binding domain, which makes it more resistant to degradation than native somatostatin. Like somatostatin, octreotide has a broad range of antisecretory actions mediated by membrane receptors. In patients with acromegaly, it inhibits GH secretion and subsequently **reduces IGF-1 release**, which can mitigate many of the clinical manifestations of the disease. It also exerts an anti-proliferative effect on somatotroph cells and helps **reduce residual adenoma size** in many patients **(Choice E)**.

(Choices B and D) Pegvisomant is a competitive inhibitor of GH that blocks the binding of GH to its receptor. This drug reduces GH-induced IGF-1 secretion and the subsequent downstream effects but does

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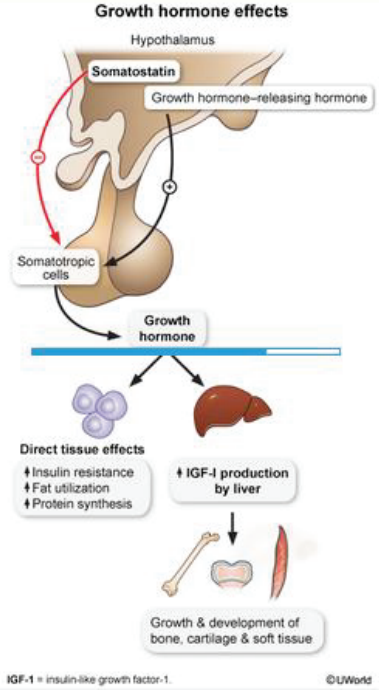


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proliferative effect on somatotroph cells and helps **reduce residual adenoma size** in many patients **(Choice E)**.

(Choices B and D) Pegvisomant is a competitive inhibitor of GH that blocks the binding of GH to its receptor. This drug reduces GH-induced IGF-1 secretion and the subsequent downstream effects but does not alter GH secretion. Adenoma size may remain stable or increase somewhat.

(Choice C) Medical treatment (eg, octreotide) is indicated for patients with incompletely resected somatotroph adenomas because, without treatment, the residual tissue will likely continue to grow and secrete GH, inducing a rise in IGF-1 levels.

Educational objective:
Acromegaly is usually treated with resection of the somatotroph pituitary adenoma, but additional medical therapy is needed for patients with residual tumor. Octreotide is a long-acting somatostatin analogue that inhibits growth hormone secretion and, subsequently, insulin-like growth factor-1 release. It also reduces residual adenoma size in many patients.

Pharmacology	Endocrine, Diabetes & Metabolism	Acromegaly
Subject	System	Topic

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A 26-year-old pregnant woman at 16 weeks gestation comes to the office for prenatal follow-up. The patient has a 2-year history of mild hyperthyroidism due to Graves disease and started taking propylthiouracil when she decided to attempt pregnancy. The patient has had no tremulousness, palpitations, diarrhea, or heat intolerance. She has no other medical problems and no drug allergies. She takes a prenatal vitamin. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/60 mm Hg, and pulse is 88/min. Physical examination reveals no lid lag, exophthalmos, or hand tremors. The thyroid gland is normal to palpation. Fetal heart rate is normal. Thyroid hormone levels are within the laboratory's reference ranges. During this visit, her thyroid treatment is changed from propylthiouracil to methimazole. Switching the patient's therapy at this time is aimed at decreasing which of the following complications?

A. Fetal skin abnormalities
B. Fetal thyroid agenesis
C. Maternal hepatotoxicity
D. Maternal ophthalmopathy
E. Maternal thyroid cancer

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patient has a 2-year history of mild hyperthyroidism due to Graves disease and started taking propylthiouracil when she decided to attempt pregnancy. The patient has had no tremulousness, palpitations, diarrhea, or heat intolerance. She has no other medical problems and no drug allergies. She takes a prenatal vitamin. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/60 mm Hg, and pulse is 88/min. Physical examination reveals no lid lag, exophthalmos, or hand tremors. The thyroid gland is normal to palpation. Fetal heart rate is normal. Thyroid hormone levels are within the laboratory's reference ranges. During this visit, her thyroid treatment is changed from propylthiouracil to methimazole. Switching the patient's therapy at this time is aimed at decreasing which of the following complications?

A. Fetal skin abnormalities
B. Fetal thyroid agenesis
C. Maternal hepatotoxicity
D. Maternal ophthalmopathy
E. Maternal thyroid cancer

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palpitations, diarrhea, or heat intolerance. She has no other medical problems and no drug allergies. She takes a prenatal vitamin. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/60 mm Hg, and pulse is 88/min. Physical examination reveals no lid lag, exophthalmos, or hand tremors. The thyroid gland is normal to palpation. Fetal heart rate is normal. Thyroid hormone levels are within the laboratory's reference ranges. During this visit, her thyroid treatment is changed from propylthiouracil to methimazole. Switching the patient's therapy at this time is aimed at decreasing which of the following complications?

A. Fetal skin abnormalities (16%)
B. Fetal thyroid agenesis (38%)
C. Maternal hepatotoxicity (43%)
D. Maternal ophthalmopathy (0%)
E. Maternal thyroid cancer (0%)

Correct
43%
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02/07/2021

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Thionamide **antithyroid drugs** (eg, propylthiouracil [PTU], methimazole) are used to decrease thyroid hormone production. In Graves disease, they can be used to induce a euthyroid state in preparation for definitive treatment with radioiodine or surgery and can sometimes achieve remission in patients with mild disease.

Methimazole is preferred for most patients due the **hepatotoxicity** of PTU; PTU often causes transient elevations in hepatic transaminases and occasionally can cause severe idiosyncratic liver injury with acute liver failure. However, **methimazole** has potential **teratogenic effects** (eg, aplasia cutis **[Choice A]**, esophageal atresia, facial anomalies), so PTU is preferred in the first trimester of pregnancy. Thereafter, the patient should be returned to methimazole therapy.

(Choice B) Thyroid dysgenesis (abnormal development of the thyroid gland) can manifest as absence (agenesis), ectopic location, or hypoplasia of the thyroid gland. The thyroid gland is normally fully developed by week 12; therefore, switching from PTU to methimazole at 16 weeks gestation is unlikely to cause thyroid dysgnesis. Thionamide antithyroid drugs can cause hypothyroidism with goiter (rather than dysgenesis) in newborns, but the effects are typically transient as the drugs are cleared within days.

(Choice D) Graves ophthalmopathy is due to the activation of TSH receptors on orbital fibroblasts by thyrotropin receptor autoantibodies, which leads to the expansion of the ground substance of retro-orbital

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developed by week 12; therefore, switching from PTU to methimazole at 16 weeks gestation is unlikely to cause thyroid dysgnesis. Thionamide antithyroid drugs can cause hypothyroidism with goiter (rather than dysgenesis) in newborns, but the effects are typically transient as the drugs are cleared within days.

(Choice D) Graves ophthalmopathy is due to the activation of TSH receptors on orbital fibroblasts by thyrotropin receptor autoantibodies, which leads to the expansion of the ground substance of retro-orbital tissues and edema of the extraocular muscles. Radioiodine therapy for Graves disease can acutely worsen ophthalmopathy, but this is less of a concern with antithyroid drugs.

(Choice E) Risk factors for thyroid cancer include exposure to ionizing radiation, iodine-deficient diet, and certain familial cancer syndromes (eg, familial adenomatous polyposis). Antithyroid drugs do not increase the risk for thyroid cancer.

Educational objective:
Thionamide antithyroid drugs (eg, propylthiouracil [PTU], methimazole) are used to decrease thyroid hormone production. Methimazole is preferred for most patients due to the hepatotoxicity of PTU. However, methimazole has potential teratogenic effects, so PTU is preferred in the first trimester of pregnancy.

References

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A 46-year-old man comes to the office to follow up mixed hyperlipidemia. His lipid levels have progressively worsened over the last 10 years associated with gradual weight gain. In the last 6 months, the patient has attempted to modify his diet and exercise regimen, but his lipid levels have not improved. Past medical history is unremarkable, and he currently takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/86 mm Hg, pulse is 76/min, and BMI is 28 kg/m^2. Cardiovascular examination is normal. Which of the following drugs, when used as monotherapy, would be most likely to increase triglyceride levels in this patient?

- A. Atorvastatin
- B. Cholestyramine
- C. Ezetimibe
- D. Gemfibrozil
- E. Niacin

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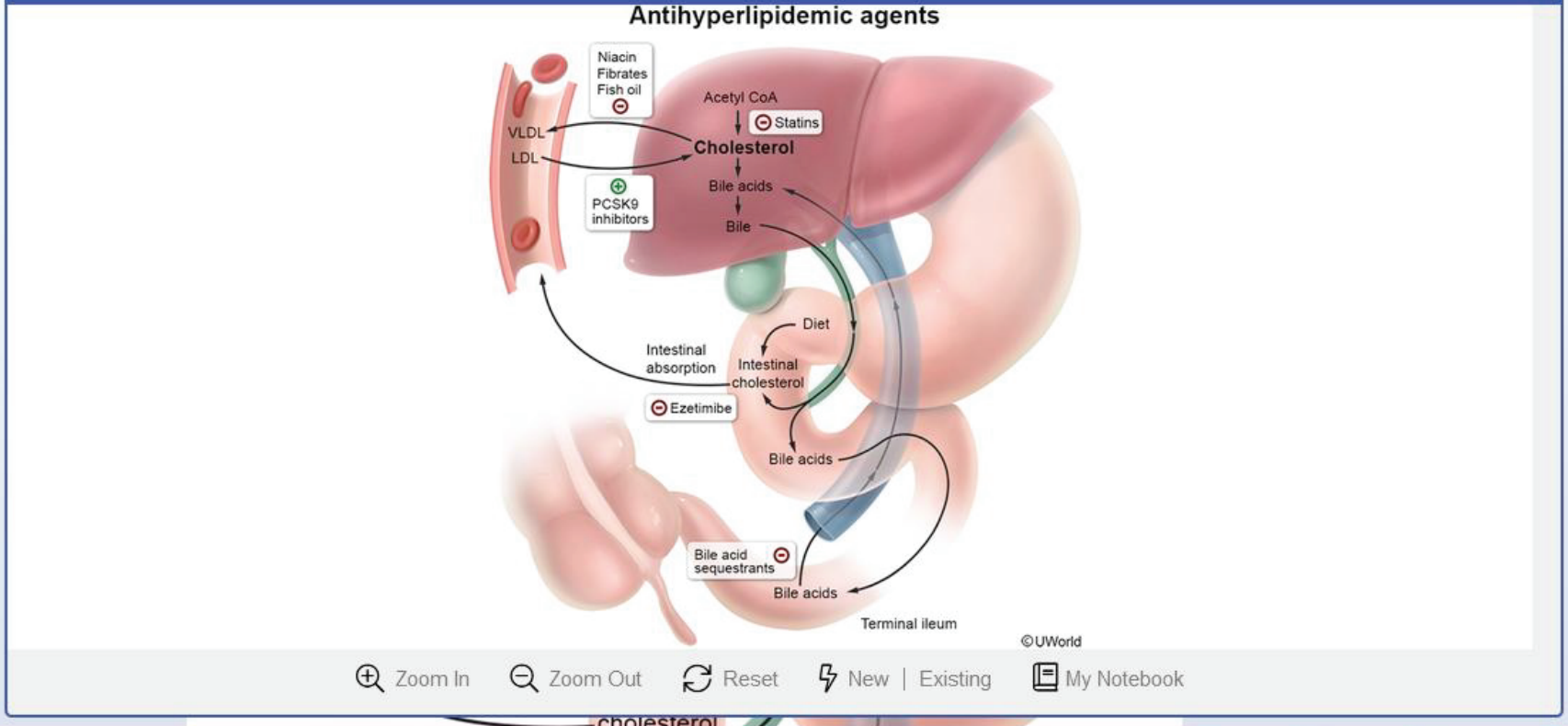
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A. Atorvastatin (6%)
B. Cholestyramine (47%)
C. Ezetimibe (13%)
D. Gemfibrozil (16%)
E. Niacin (15%)

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cholesterol

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Bile acid-binding resins (eg, cholestyramine, colestipol, colesevelam) work by binding bile acids in the gastrointestinal tract, inhibiting **enterohepatic circulation**. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of LDL cholesterol from the circulation, and reduced blood LDL levels.

The main side effects of bile acid-binding resins are gastrointestinal upset and impaired absorption of nutrients and drugs. In addition, bile acid-binding resins increase hepatic production of triglycerides and increase the release of triglyceride-heavy VLDL particles into the circulation, leading to **hypertriglyceridemia**.

(Choice A) Statins cause modest reductions in triglyceride levels by decreasing synthesis and increasing clearance of VLDL particles.

(Choice C) Ezetimibe selectively inhibits the intestinal absorption of cholesterol and lowers LDL levels. Ezetimibe does not affect triglyceride absorption but may lower blood triglyceride levels slightly.

(Choice D) Fibrates (eg, gemfibrozil, fenofibrate) inhibit hepatic production of triglycerides and are first-line treatments for hypertriglyceridemia.

(Choice E) Niacin reduces blood triglyceride levels, raises HDL levels, and decreases VLDL conversion to

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clearance of VLDL particles.

(Choice C) Ezetimibe selectively inhibits the intestinal absorption of cholesterol and lowers LDL levels. Ezetimibe does not affect triglyceride absorption but may lower blood triglyceride levels slightly.

(Choice D) Fibrates (eg, gemfibrozil, fenofibrate) inhibit hepatic production of triglycerides and are first-line treatments for hypertriglyceridemia.

(Choice E) Niacin reduces blood triglyceride levels, raises HDL levels, and decreases VLDL conversion to LDL, thereby decreasing LDL concentrations as well.

Educational objective:
Bile acid-binding resins inhibit the enterohepatic circulation of bile acids. This leads to diversion of hepatic cholesterol to synthesis of new bile acids, increased uptake of cholesterol from the circulation, and reduced blood LDL levels. However, bile acid-binding resins increase hepatic production of triglycerides and can cause hypertriglyceridemia.

Pharmacology	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

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A 19-year-old man comes to the office due to frequent episodes of disorientation, palpitations, tremulousness, and excessive sweating over the past 3 months. He says the symptoms resolve quickly after drinking some juice or a carbonated beverage. The patient was diagnosed with type 1 diabetes mellitus at age 12 and takes short- and long-acting insulin. He has had no dose changes in the past 2 years or diabetic complications and follows up with an ophthalmologist frequently. The patient is a college student and reports some stress due to an upcoming midterm examination. He does not use tobacco, alcohol, or illicit drugs. Vital signs and physical examination are within normal limits. Laboratory results show a hemoglobin A1c of 6.8% and no proteinuria. Which of the following factors most likely precipitated this patient's current symptoms?

- A. Fructose-rich drink consumption
- B. Intense exercise
- C. Mental stress
- D. Respiratory infection
- E. Sleep deprivation

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tremulousness, and excessive sweating over the past 3 months. He says the symptoms resolve quickly after drinking some juice or a carbonated beverage. The patient was diagnosed with type 1 diabetes mellitus at age 12 and takes short- and long-acting insulin. He has had no dose changes in the past 2 years or diabetic complications and follows up with an ophthalmologist frequently. The patient is a college student and reports some stress due to an upcoming midterm examination. He does not use tobacco, alcohol, or illicit drugs. Vital signs and physical examination are within normal limits. Laboratory results show a hemoglobin A1c of 6.8% and no proteinuria. Which of the following factors most likely precipitated this patient's current symptoms?

A. Fructose-rich drink consumption
B. Intense exercise
C. Mental stress
D. Respiratory infection
E. Sleep deprivation
F. Weight gain

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mellitus at age 12 and takes short- and long-acting insulin. He has had no dose changes in the past 2 years or diabetic complications and follows up with an ophthalmologist frequently. The patient is a college student and reports some stress due to an upcoming midterm examination. He does not use tobacco, alcohol, or illicit drugs. Vital signs and physical examination are within normal limits. Laboratory results show a hemoglobin A1c of 6.8% and no proteinuria. Which of the following factors most likely precipitated this patient's current symptoms?

A. ~~Fructose-rich drink consumption~~ (3%)
B. Intense exercise (32%)
C. Mental stress (43%)
D. ~~Respiratory infection~~ (2%)
E. Sleep deprivation (15%)
F. ~~Weight gain~~ (2%)

Incorrect
Correct answer

32%

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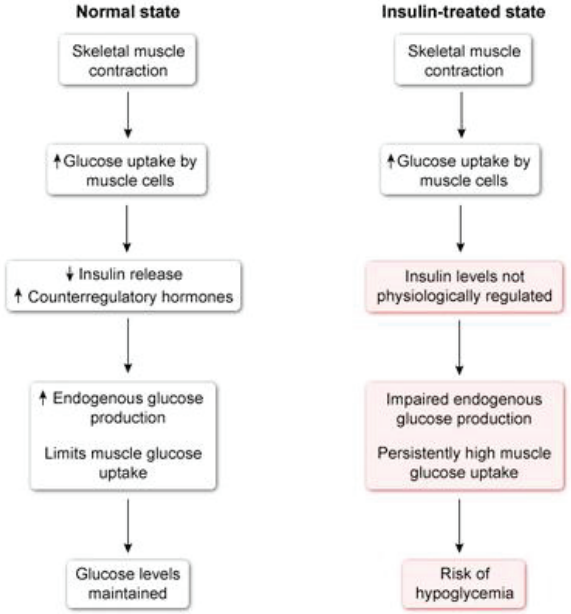
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Effect of exercise on insulin & glucose



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This patient has frequent symptomatic **hypoglycemia**—disorientation, sweating, and palpitations, which are relieved by intake of glucose—despite no changes to his chronic insulin regimen. Hypoglycemia is often induced in patients with type 1 diabetes by inadvertent overdose of insulin or decreased carbohydrate intake (eg, skipped meal), but can also be triggered by **intensive physical activity/exercise**.

Glucose uptake by skeletal muscle cells is mediated by glucose transporter type 4 (**GLUT4**). GLUT4 is **translocated to cell membranes** and transverse tubules (deep invaginations in the cell membrane) in response to **insulin**. GLUT4 translocation also occurs during **muscle contraction** by an insulin-independent mechanism, which is mediated by several cellular factors, including AMP-activated kinase, nitric oxide, and calcium-calmodulin–activated protein kinase.

In normal individuals, overt hypoglycemia does not occur with exercise because a drop in blood glucose suppresses insulin release from the beta cells, and counterregulatory hormones (eg, glucagon) increase endogenous glucose production via glycogenolysis and gluconeogenesis. However, patients taking **exogenous insulin** are vulnerable to exercise-induced hypoglycemia because insulin will **continue to be released** from the injection site despite falling glucose levels.

(Choice A) Patients with hereditary fructose intolerance cannot break down fructose and develop hypoglycemia and vomiting after ingestion of fructose-containing foods. However, this typically presents at

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released from the injection site despite falling glucose levels.

(Choice A) Patients with hereditary fructose intolerance cannot break down fructose and develop hypoglycemia and vomiting after ingestion of fructose-containing foods. However, this typically presents at the age of weaning (when fructose is introduced) and patients often develop a protective distaste for sweets. Ingestion of fructose-containing juice and soda would worsen the hypoglycemia, not correct it.

(Choices C, D, and E) Infection, pain, sleep deprivation, and severe mental/emotional distress tend to cause hyper- rather than hypoglycemia due to increased production of counterregulatory hormones (eg, catecholamines, cortisol). These hormones raise glucose by increasing glycogenolysis and gluconeogenesis and decreasing pancreatic insulin secretion (in patients with residual islet cell function).

(Choice F) Weight gain is associated with insulin resistance. Insulin-treated patients who gain weight usually develop hyperglycemia and require increased doses of insulin to maintain control of glucose.

Educational objective:
Uptake of glucose by skeletal muscle is mediated by the glucose transporter type 4, which is translocated to the cell membrane in response to insulin and muscle contraction. Hypoglycemia can be precipitated by exercise in patients with insulin-treated diabetes due to the persistent effects of exogenous insulin.

References

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A 26-year-old woman comes to the clinic due to worsening generalized weakness, myalgias, and unintentional weight loss. She has primary hypothyroidism for which she takes levothyroxine. Blood pressure is 110/70 mm Hg supine and 90/60 mm Hg standing. She appears mildly emaciated. Cardiopulmonary examination reveals no abnormalities. Laboratory studies show mild normochromic, normocytic anemia; eosinophil count of 15%; and serum glucose of 65 mg/dL. Which of the following additional changes is most likely in this patient?

	Serum Na	Serum K	Urine Na	Urine K
A.	↓	↑	↑	↓
B.	↓	Normal	↑	Normal
C.	↓	↓	↓	↑
D.	↓	↑	↓	↑
E.	Normal	↓	Normal	↑

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A 26-year-old woman comes to the clinic due to worsening generalized weakness, myalgias, and unintentional weight loss. She has primary hypothyroidism for which she takes levothyroxine. Blood pressure is 110/70 mm Hg supine and 90/60 mm Hg standing. She appears mildly emaciated. Cardiopulmonary examination reveals no abnormalities. Laboratory studies show mild normochromic, normocytic anemia; eosinophil count of 15%; and serum glucose of 65 mg/dL. Which of the following additional changes is most likely in this patient?

	Serum Na	Serum K	Urine Na	Urine K	
✓ A.	↓	↑	↑	↓	(55%)
B.	↓	~~Normal~~	↑	~~Normal~~	(11%)
C.	↓	↓	↓	↑	(13%)
D.	↓	↑	↓	↑	(9%)
E.	~~Normal~~	↓	~~Normal~~	↑	(10%)

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Explanation

This patient has multiple clinical features that suggest **primary adrenal insufficiency** (PAI) (also known as Addison disease). PAI most commonly results from autoimmune destruction of the bilateral adrenal cortex and often occurs in patients with a preexisting history of **autoimmune disease** (eg, hypothyroidism, type 1 diabetes mellitus). Reduced mineralocorticoid (mainly aldosterone) production leads to renal salt wasting with consequent **hypovolemia and orthostasis** (systolic blood pressure decrease ≥20 mm Hg with standing). Reduced cortisol can lead to **hypoglycemia**, normocytic **anemia**, and **eosinophilia**.

In the renal collecting tubule principal cells, reduced aldosterone leads to markedly decreased sodium absorption and increased potassium absorption; therefore, there is **high urine sodium** and **low urine potassium**. Serum potassium is elevated **(hyperkalemia)** due to the increased tubular absorption. Although the tubular salt wasting reduces total body sodium, it does not directly affect serum sodium concentration. However, because hypovolemia provides nonosmotic stimulus for antidiuretic hormone (ADH) secretion and ADH secretion is normally inhibited by cortisol, ADH levels are increased in PAI. The increased ADH levels lead to increased water retention and low serum sodium **(hyponatremia)**.

(Choice B) Hyponatremia in the setting of high urine sodium is characteristic of the syndrome of inappropriate ADH secretion (SIADH). SIADH has no significant effect on serum and urine potassium

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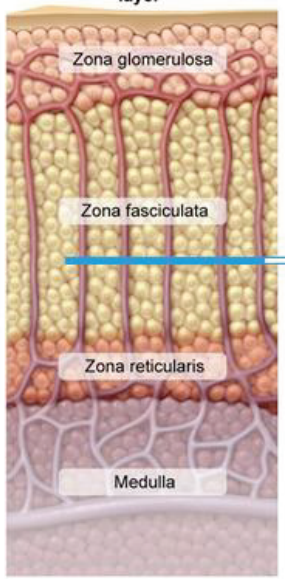
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Explanation

Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		



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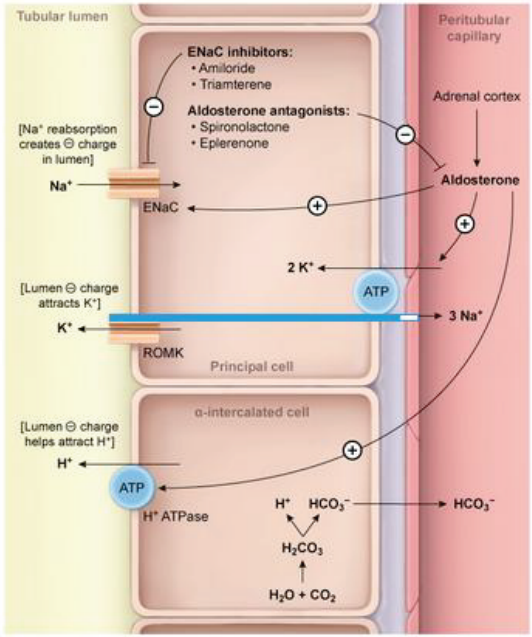
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Explanation

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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(Choices C and D) In hypovolemic states (eg, severe vomiting, diabetic ketoacidosis), restoration of blood volume is the highest priority. Therefore, the kidneys respond by stimulating increased aldosterone secretion, which decreases urine sodium and increases urine potassium. The hypovolemia also provides nonosmotic stimulus for ADH release, which leads to hyponatremia. Both total body and serum potassium are low in severe vomiting due to both gastrointestinal and renal losses. Although total body potassium is low in diabetic ketoacidosis, serum potassium is high because potassium is unable to enter cells in the absence of insulin.

(Choice E) Primary hyperaldosteronism causes potassium wasting by the renal principal cells, leading to high urine potassium and low serum potassium (hypokalemia). There is renal sodium retention that leads to increased blood volume, but any significant change in serum or urine sodium concentration is avoided due to aldosterone escape.

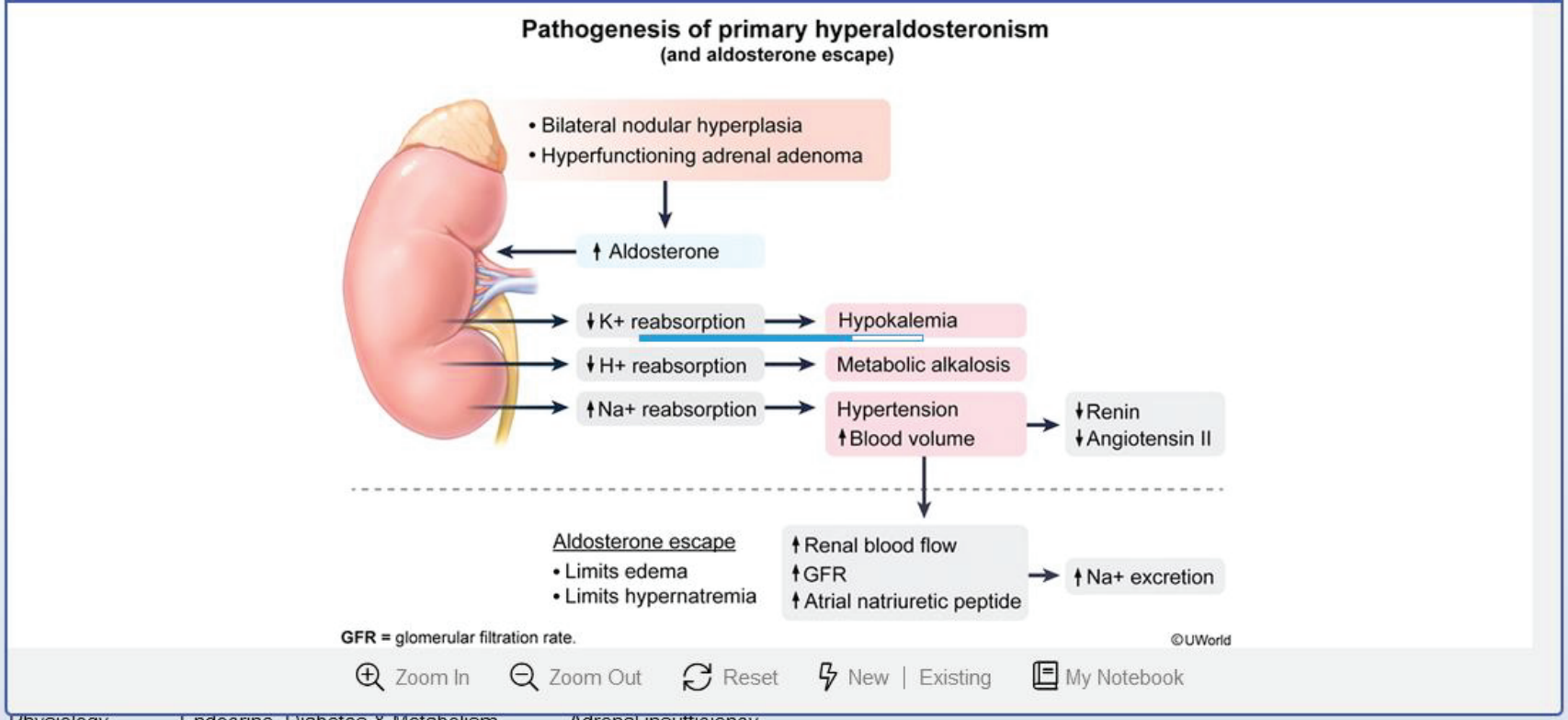
Educational objective:
Reduced aldosterone production in primary adrenal insufficiency leads to renal sodium wasting with consequent hypovolemia, orthostasis, and potassium retention (hyperkalemia). Low cortisol stimulates increased antidiuretic hormone secretion, which leads to water retention and hyponatremia.

Physiology Endocrine, Diabetes & Metabolism Adrenal insufficiency

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(Choices C and D) In hypovolemic states (eg, severe vomiting, diabetic ketoacidosis), restoration of blood

Exhibit Display



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Physiology | Endocrine, Diabetes & Metabolism | Adrenal insufficiency

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A 56-year-old man comes to the office for follow-up of type 2 diabetes mellitus. The patient has had inadequate glycemic control with metformin monotherapy, and a new medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. He feels well and reports no adverse effects from the new therapy. The patient also has hypertension, for which he takes ramipril. He does not use tobacco, alcohol, or illicit drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast foods. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following direct mechanisms?

A. Decreased dietary carbohydrate digestion
B. Decreased renal glucose reabsorption
C. Increased glucagon secretion
D. Increased glucose-dependent insulin release
E. Increased peripheral tissue glucose uptake

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inadequate glycemic control with metformin monotherapy, and a new medication that inhibits dipeptidyl peptidase-4 was prescribed 3 months ago. He feels well and reports no adverse effects from the new therapy. The patient also has hypertension, for which he takes ramipril. He does not use tobacco, alcohol, or illicit drugs. The patient says he is generally compliant with dietary guidance but occasionally eats fast foods. Blood pressure is 126/74 mm Hg and pulse is 76/min. BMI is 31.4 kg/m^2. Physical examination shows no abnormalities. Laboratory results show a hemoglobin A1c of 6.8%. The newly prescribed medication most likely improved this patient's glycemic control through which of the following direct mechanisms?

A. Decreased dietary carbohydrate digestion (7%)

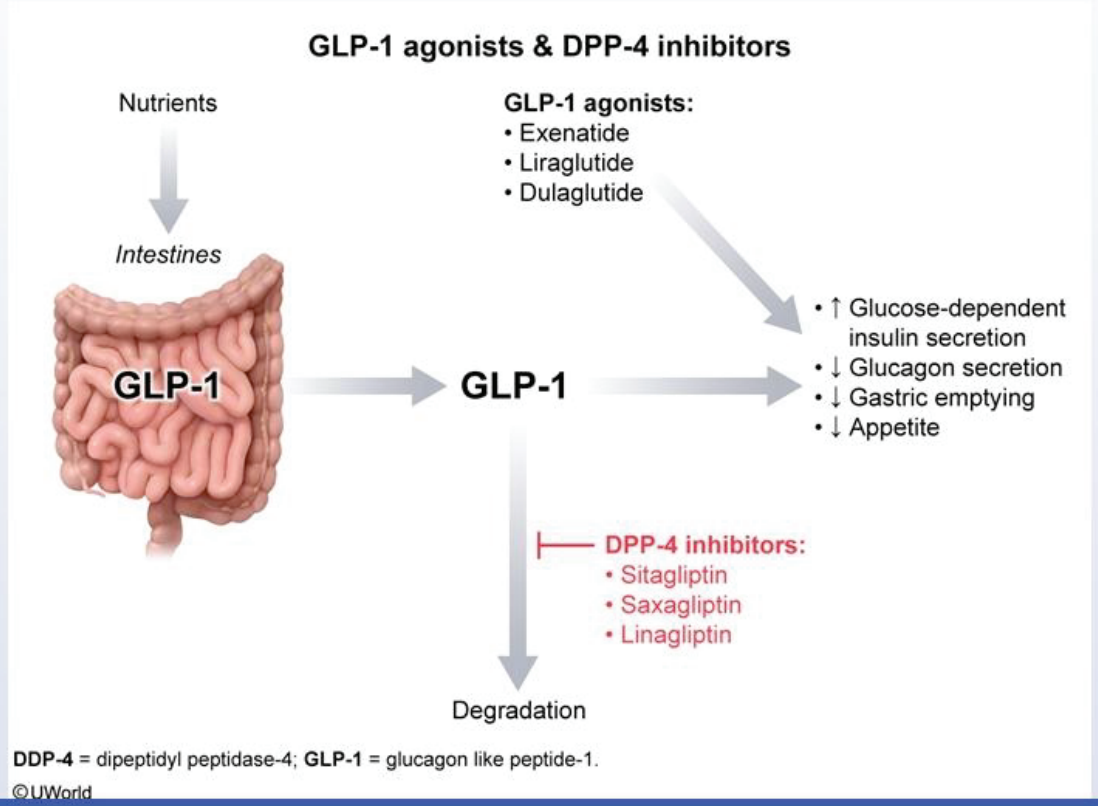
B. ~~Decreased renal glucose reabsorption~~ (2%)

C. ~~Increased glucagon secretion~~ (5%)

✓ D. Increased glucose-dependent insulin release (69%)

E. ~~Increased peripheral tissue glucose uptake~~ (14%)

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Glucagon-like peptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake and regulates glucose levels by slowing gastric emptying, suppressing glucagon secretion, and **increasing glucose-dependent insulin release**. It acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system. Native GLP-1 is degraded by dipeptidyl peptidase-4 (DPP-4).

DPP-4 inhibitors (eg, sitagliptin, saxagliptin) **inhibit the degradation of GLP-1**, prolonging its effects and leading to improved glycemic control (eg, reduction in hemoglobin A1c). GLP-1's effect on insulin secretion is glucose-dependent: as glucose levels fall, so does insulin secretion. Therefore, DPP-4 inhibitors have a **low risk of hypoglycemia**. Major side effects include nasopharyngitis and other upper respiratory symptoms.

GLP-1 agonists that are intrinsically resistant to degradation by DPP-4 are also available and have a similar (but more potent) effect in lowering blood glucose with a low risk of hypoglycemia.

(Choice A) Alpha-glucosidase inhibitors (eg, acarbose) directly impair the hydrolysis of polymeric carbohydrates, leading to decreased postprandial glucose absorption. Although DPP-4 inhibitors can indirectly slow digestion of carbohydrates due to delayed gastric emptying, they do not directly affect intestinal carbohydrate metabolism.

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carbohydrates, leading to decreased postprandial glucose absorption. Although DPP-4 inhibitors can indirectly slow digestion of carbohydrates due to delayed gastric emptying, they do not directly affect intestinal carbohydrate metabolism.

(Choice B) Sodium-glucose cotransporter-2 inhibitors (eg, canagliflozin, dapagliflozin) act in the kidney to decrease reabsorption of filtered glucose.

(Choice C) GLP-1 acts directly on pancreatic islet cells to suppress glucagon secretion, an effect that is enhanced by DPP-4 inhibitors.

(Choice E) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase.

Educational objective:
Glucagon-like peptide-1 (GLP-1) regulates glucose by slowing gastric emptying, suppressing glucagon secretion, and increasing glucose-dependent insulin release. Dipeptidyl peptidase-4 inhibitors (eg, sitagliptin, saxagliptin) decrease the breakdown of GLP-1 and improve glycemic control in patients with type 2 diabetes. Because the effect on insulin is glucose-dependent, these medications have a low risk of hypoglycemia.

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A 17-year-old girl is brought to the clinic due to irregular menses. Menarche was at age 12 and her cycles since then have been irregular, often with multiple months between menstrual periods. The patient also has had an increase in hair growth along her chest and face. Temperature is 37.3 C (99.1 F), blood pressure is 110/70 mm Hg, and pulse is 80/min. There are dark, terminal hairs above the patient's upper lip and nodulocystic acne across her forehead. Cardiopulmonary examination is normal. Sexual maturity rating (Tanner stage) is 5. Ultrasound examination of the pelvis reveals a normal uterus and ovaries. Electrolytes are normal; other laboratory results are as follows:

Testosterone, serum	400 ng/dL	(normal: 25-75 ng/dL)
17-hydroxyprogesterone	350 ng/dL	(normal: <200 ng/dL)

Which of the following enzyme reaction steps is most likely to be disrupted in this patient?

A. 11-deoxycorticosterone conversion to corticosterone

B. 11-deoxycortisol conversion to cortisol

C. Pregnenolone conversion to 17-hydroxypregnenolone

D. Progesterone conversion to 11-deoxycorticosterone

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A. 11-deoxycorticosterone conversion to corticosterone
B. 11-deoxycortisol conversion to cortisol
C. Pregnenolone conversion to 17-hydroxypregnenolone
D. Progesterone conversion to 11-deoxycorticosterone
E. Testosterone conversion to estradiol

Submit

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lip and nodulocystic acne across her forehead. Cardiopulmonary examination is normal. Sexual maturity rating (Tanner stage) is 5. Ultrasound examination of the pelvis reveals a normal uterus and ovaries. Electrolytes are normal; other laboratory results are as follows:

Testosterone, serum	400 ng/dL	(normal: 25-75 ng/dL)
17-hydroxyprogesterone	350 ng/dL	(normal: <200 ng/dL)

Which of the following enzyme reaction steps is most likely to be disrupted in this patient?

A. ~~11-deoxycorticosterone conversion to corticosterone~~ (12%)
B. 11-deoxycortisol conversion to cortisol (11%)
C. ~~Pregnenolone conversion to 17-hydroxypregnenolone~~ (9%)
D. Progesterone conversion to 11-deoxycorticosterone (38%)
E. Testosterone conversion to estradiol (27%)

Incorrect
Correct answer

38%
03 mins, 10 secs
09/20/2020

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Explanation

21-Hydroxylase deficiency clinical syndromes			
	Classic, salt wasting	**Classic, non–salt wasting***	**Nonclassic, late onset**
Enzyme deficiency	Severe	Moderate	Mild
Clinical features	• Birth (girls): ambiguous genitalia • Age 1-2 weeks: vomiting, hypotension, hyperkalemia	• Birth (girls): ambiguous genitalia • Age 2-4: virilization (eg, body odor, pubic/axillary hair) & rapid growth	• School-aged: premature pubarche & rapid growth • Adolescence (girls): hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		

*Also called simple virilizing form

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	vomiting, hypotension, hyperkalemia	body odor, pubic/axillary hair) & rapid growth	hirsutism, acne, oligomenorrhea
Laboratory features	• Increased 17-hydroxyprogesterone • Increased testosterone		
*Also called simple virilizing form.			

This patient's laboratory findings are consistent with **21-hydroxylase deficiency**, the most common cause of congenital adrenal hyperplasia (CAH). The 21-hydroxylase enzyme is responsible for conversion of **progesterone to 11-deoxycorticosterone** and 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Enzyme deficiency causes the **buildup of 17-OHP**, which is then shunted toward androgen production.

Deficiency of 21-hydroxylase can result in varying clinical phenotypes depending on the amount of residual enzyme available. This patient's presentation in **adolescence** with **menstrual irregularities** and signs of **androgen excess** (ie, hirsutism, nodulocystic acne) is consistent with the mildest form, **nonclassic** (late-onset) CAH. Other common findings of nonclassic CAH include premature pubarche (ie, early appearance of pubic/axillary hair) and accelerated growth and bone age in school-aged children. Because 21-hydroxylase is not completely absent in nonclassic CAH, sufficient mineralocorticoids are produced to avoid the salt wasting (ie, hypotension, hyperkalemia) seen in neonates with severe classic CAH.

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Laboratory studies in all forms of 21-hydroxylase deficiency reveal **elevated 17-OHP and testosterone** levels.

(Choices A and B) Patients with 11 beta-hydroxylase deficiency have impaired conversion of 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. In addition to hyperandrogenism, patients have hypertension and hypokalemia (not seen here) due to increased 11-deoxycorticosterone (a weak mineralocorticoid).

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-

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deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. In addition to hyperandrogenism, patients have hypertension and hypokalemia (not seen here) due to increased 11-deoxycorticosterone (a weak mineralocorticoid).

(Choice C) Conversion of pregnenolone to 17-hydroxypregnenolone is impaired with 17 alpha-hydroxylase deficiency. Patients have hypertension and hypokalemia due to increased mineralocorticoid synthesis and amenorrhea and absent secondary sexual characteristics due to absent sex hormone production. In addition, 17-OHP and testosterone are decreased with this disorder.

(Choice E) Aromatase converts testosterone to estradiol. Due to lack of estrogens, aromatase deficiency results in primary amenorrhea, absent breast development, and virilized genitalia (eg, clitoromegaly) in girls.

Educational objective:

Nonclassic congenital adrenal hyperplasia is due to mild deficiency of 21-hydroxylase, an enzyme that converts progesterone to 11-deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol. In adolescent girls, it presents with signs of hyperandrogenism (eg, hirsutism, acne, menstrual irregularities) as well as increased 17-hydroxyprogesterone and testosterone levels.

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A 42-year-old man with a long history of type 1 diabetes mellitus comes to the office due to frequent involuntary loss of urine. For the past several months, he has been having difficulty starting and maintaining a urinary stream. In the last 3 weeks, he has had 2 episodes of nocturnal enuresis and multiple daytime episodes of uncontrolled voiding without any sensation of a full bladder. His other medical problems include chronic kidney disease and gastroparesis. He does not use tobacco or alcohol. Which of the following additional findings would most likely be present in this patient?

A. Enlarged prostate on rectal examination
B. Increased postvoid residual volume
C. Loss of sensation in perineal area
D. Lower extremity hyperreflexia
E. Mini-mental state examination score of 22

Submit

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A 42-year-old man with a long history of type 1 diabetes mellitus comes to the office due to frequent involuntary loss of urine. For the past several months, he has been having difficulty starting and maintaining a urinary stream. In the last 3 weeks, he has had 2 episodes of nocturnal enuresis and multiple daytime episodes of uncontrolled voiding without any sensation of a full bladder. His other medical problems include chronic kidney disease and gastroparesis. He does not use tobacco or alcohol. Which of the following additional findings would most likely be present in this patient?

A. Enlarged prostate on rectal examination (12%)
B. Increased postvoid residual volume (41%)
C. Loss of sensation in perineal area (36%)
D. Lower extremity hyperreflexia (8%)
E. Mini-mental state examination score of 22 (0%)

Correct

41% Answered correctly

58 secs Time Spent

10/03/2020 Last Updated

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This patient's findings suggest **overflow incontinence**, which is mainly due to **impaired detrusor contractility** or **bladder outlet obstruction** (eg, tumor obstructing the urethra). Patients usually develop involuntary and continuous urinary leakage when the bladder is full and often have incomplete emptying. This patient's overflow incontinence is most likely due to diabetic autonomic neuropathy affecting detrusor muscle innervation, which is common in type 1 diabetics.

Patients initially have infrequent urination due to loss of autonomic afferent innervation and inability to sense a full bladder. Involvement of efferent fibers to the bladder subsequently causes incomplete emptying. Patients can develop recurrent urinary tract infections (UTIs) and overflow incontinence with poor urinary stream and dribbling. Pelvic floor relaxation at night combined with a full bladder can lead to nocturnal enuresis. Postvoid residual (PVR) testing with ultrasound or catheterization can confirm inadequate bladder emptying.

(Choice A) Enlarged prostate on rectal examination may indicate either benign prostatic hyperplasia or prostate cancer, which causes urge incontinence (bladder irritation from the enlarged prostate) or overflow incontinence (urethral obstruction). However, these conditions are commonly seen in older individuals (age >50-60).

(Choice C) Loss of sensation in the perineal area (saddle anesthesia) can indicate cauda equina

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>50-60).

(Choice C) Loss of sensation in the perineal area (saddle anesthesia) can indicate cauda equina syndrome, which is commonly due to epidural cord compression from a malignancy. Patients usually develop urinary retention late in the course of the disease, usually associated with fecal incontinence.

(Choices D and E) Cognitive impairment (mini-mental status examination score ≤22) is often seen in normal pressure hydrocephalus, and lower extremity hyperreflexia would suggest spinal cord disease. Both of these conditions can cause loss of central nervous system inhibition of detrusor contraction, leading to urge incontinence. Urge incontinence is characterized by a sudden desire to urinate. However, absence of other symptoms (eg, gait disturbance) in this patient makes these conditions less likely.

Educational objective:
Diabetic autonomic neuropathy is common in type 1 diabetics and can cause overflow incontinence due to inability to sense a full bladder and incomplete emptying. Postvoid residual (PVR) testing with ultrasound or catheterization can confirm inadequate bladder emptying.

References

- Diagnosis of urinary incontinence.

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A 32-year-old woman comes to the office due to a persistent sensation of warmth. For the last 6 months she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m^2. On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

A. Thyroglobulin
B. Thyroid peroxidase
C. Thyrotropin receptor
D. Thyroxine
E. Triiodothyronine

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she has felt unusually warm compared to others in the room. The patient has no medical problems and takes no medications or supplements. She does not use tobacco, alcohol, or illicit drugs. Family history is significant for hypothyroidism in her mother. Temperature is 36.7 C (98 F), blood pressure is 130/60 mm Hg, and pulse is 104/min. BMI is 20 kg/m^2. On physical examination, the patient appears anxious and has a staring gaze. There is exophthalmos, lid lag, and a diffusely enlarged thyroid with an audible thyroid bruit. The patient has a fine tremor on outstretched arms, and the skin is warm and moist. Antibodies directed against which of the following are most likely to be found in this patient?

A. ~~Thyroglobulin~~ (9%)
B. ~~Thyroid peroxidase~~ (12%)
✓ C. Thyrotropin receptor (77%)
D. Thyroxine (0%)
E. Triiodothyronine (0%)

Correct
77%
01 min, 32 secs
01/01/2021

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Thyroid autoantibodies	
Antibody	**Disease association**
Thyrotropin (TSH) receptor antibody	• **Graves disease** • Functional bioassay (thyroid-stimulating immunoglobulin) is also available
Thyroid peroxidase antibody	• **Chronic lymphocytic (Hashimoto) thyroiditis** • Silent thyroiditis • Postpartum thyroiditis • Some patients with Graves disease
Thyroglobulin antibody	• Nonspecific, but more common in hypothyroidism than hyperthyroidism

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including

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	hyperthyroidism

This patient has signs of hyperthyroidism, including heat intolerance, tachycardia, and lid lag. In light of her diffuse goiter and exophthalmos this is very likely due to **Graves disease**. Graves disease is an autoimmune disorder triggered by **thyrotropin receptor antibodies** (TRAb), which bind and activate the TSH receptor. In addition to the thyroid, the TSH receptor antigen is present on other cell types, including fibroblasts and adipocytes. Graves ophthalmopathy is characterized by ocular irritation, impaired extraocular motion, and proptosis; it is caused by T-cell activation and stimulation of orbital fibroblasts by TRAb, leading to expansion of extraocular muscles and retro-orbital tissues.

TRAb binds to extracellular domains on the TSH receptor, a transmembrane G protein–coupled receptor. The G_s alpha subunit activates adenylate cyclase and subsequently the adenylate cyclase second messenger system. Serum TRAb immunoassays have a high sensitivity (97%) and specificity (99%) for Graves disease, although they detect both activating and blocking anti-TSH receptor antibodies. Activating antibodies can be confirmed with a functional bioassay (thyroid-stimulating immunoglobulin) that measures cyclic AMP production by a TSH-receptor–expressing cell line in response to patient serum.

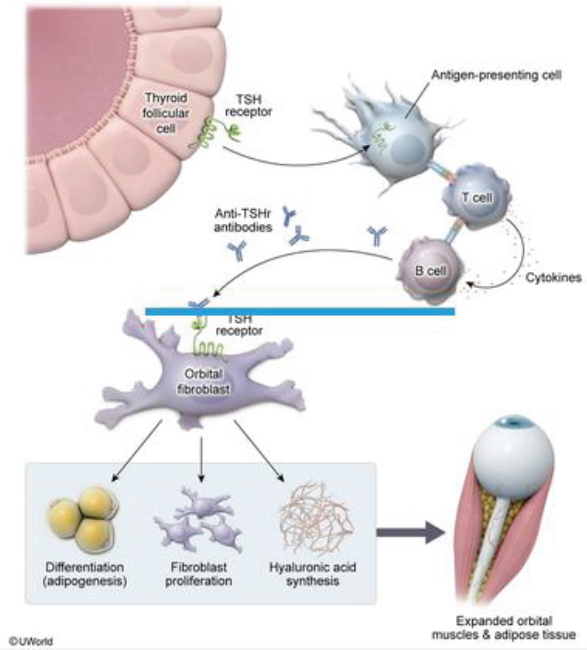
(Choice A) Antibodies to thyroglobulin are thought to reflect disruption of thyroid follicles, which exposes thyroglobulin to the bloodstream. They are present in a number of autoimmune thyroid disorders but are

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hyperthyroidism

Exhibit Display

Pathogenesis of Graves ophthalmopathy



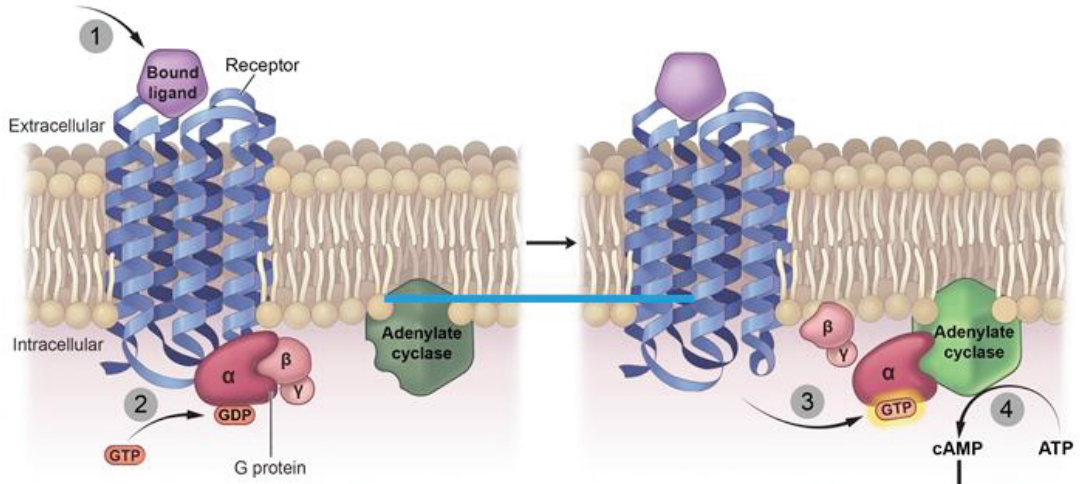
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hyperthyroidism

Exhibit Display

G protein activation of adenylate cyclase



cAMP = cyclic AMP; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate.

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(Choice A) Antibodies to thyroglobulin are thought to reflect disruption of thyroid follicles, which exposes thyroglobulin to the bloodstream. They are present in a number of autoimmune thyroid disorders but are most common in autoimmune hypothyroidism and are present in only a minority of patients with Graves disease.

(Choice B) Thyroid peroxidase antibodies are most closely associated with Hashimoto thyroiditis and related disorders (eg, silent thyroiditis, postpartum thyroiditis). Hyperthyroidism with exophthalmos is most consistent with Graves disease.

(Choices D and E) Antibodies to thyroxine and triiodothyronine (ie, anti-T4 and anti-T3 immunoglobulins, respectively) can be detected by adding radiolabeled thyroid hormone to the patient's serum followed by precipitation of the antigen-antibody complexes with polyethylene glycol. These antibodies can be seen in a variety of autoimmune thyroid disorders, but are rare.

Educational objective:
Graves disease is an autoimmune disorder triggered by thyrotropin receptor antibodies (TRAb) that bind and activate the TSH receptor. Serum TRAb immunoassays have a high sensitivity and specificity for Graves disease.

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A 27-year-old man comes to the office for an infertility evaluation. He and his wife have been trying to conceive for the last 16 months. A previous evaluation of his wife showed no abnormalities. The patient has no prior medical conditions and takes no medications. Height is 188 cm (6' 2") and weight is 75 kg (165.3 lb). BMI is 21 kg/m^2. On physical examination, heart and lung sounds are normal. There is bilateral gynecomastia, and genital examination shows small, firm testes. The lower extremities appear abnormally long. Further evaluation will most likely show which of the following sets of findings in this patient?

	Serum LH	Serum FSH	Serum testosterone	Sperm count
A.	Decreased	Decreased	Decreased	Decreased
B.	Normal	Normal	Normal	Absent
C.	Decreased	Normal	Increased	Decreased
D.	Increased	Increased	Decreased	Absent
E.	Normal	Increased	Normal	Decreased

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	Serum LH	Serum FSH	Serum testosterone	Sperm count	
✗ A.	Decreased	Decreased	Decreased	Decreased	(21%)
B.	Normal	Normal	Normal	Absent	(1%)
C.	Decreased	Normal	Increased	Decreased	(2%)
✓ D.	Increased	Increased	Decreased	Absent	(68%)
E.	Normal	Increased	Normal	Decreased	(5%)

Incorrect

68%

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12/04/2020

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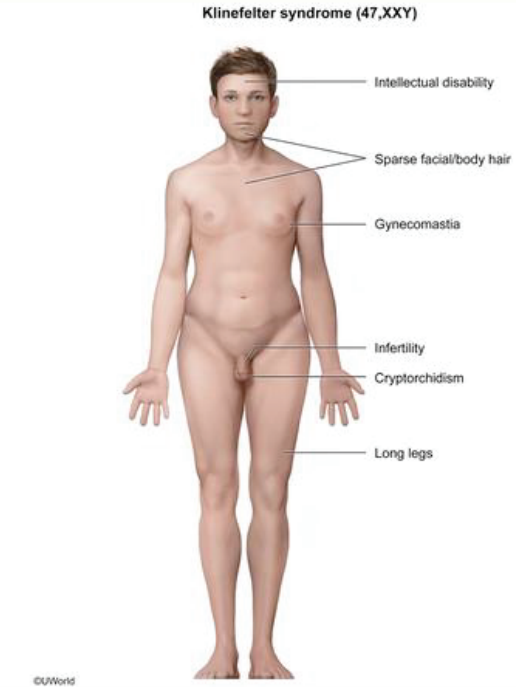
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This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**. Klinefelter syndrome is a chromosomal disorder (47,XXY) that can lead to **azoospermia** and infertility, although individuals with mosaic variants may have variable degrees of spermatogenesis. Common nonreproductive manifestations include intellectual and language impairment.

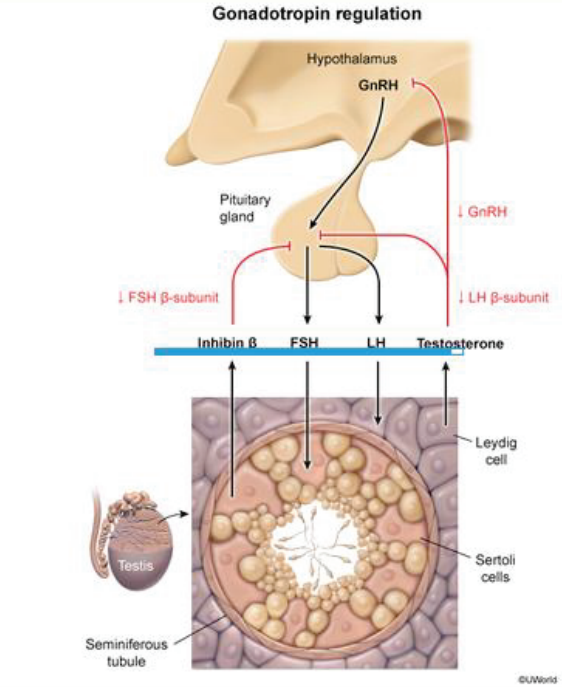
Klinefelter syndrome is the most common cause of male hypogonadism and is characterized by progressive destruction and hyalinization of the seminiferous tubules, leading to small, firm testes. Serum **inhibin levels are decreased** as a result of the Sertoli cell damage; Leydig cells are usually dysfunctional as well, resulting in **reduced testosterone** levels. The loss of feedback inhibition leads to **increased FSH and LH secretion**. Gynecomastia is caused by an increased ratio of estrogens to androgens (high gonadotropin levels increase aromatase activity, which increases conversion of testosterone to estradiol).

(Choice A) Hypogonadotropic (central) hypogonadism is caused by injury or dysfunction of the hypothalamus (eg, Kallmann syndrome) or pituitary gland (eg, adenomas). LH, FSH, and testosterone levels are all low, and spermatogenesis is impaired. Unlike in this patient, testes in central hypogonadism are atrophic and soft (not hyalinized and firm), and gynecomastia is uncommon because the decrease in gonadotropins reduces aromatase activity.

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gonadotropins reduces aromatase activity.

(Choice B) Azoospermia associated with a normal hormonal profile suggests an obstruction along the path from the testes to the seminal fluid (eg, congenital absence of the vas deferens in cystic fibrosis). In these patients, the testes and breasts are grossly normal.

(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:
Klinefelter syndrome (47,XXY) causes infertility characterized by primary hypogonadism (elevated FSH and LH, low testosterone) and azoospermia. Other findings include long lower extremities; small, firm testes;

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(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:

Klinefelter syndrome (47,XXY) causes infertility characterized by primary hypogonadism (elevated FSH and LH, low testosterone) and azoospermia. Other findings include long lower extremities; small, firm testes; and gynecomastia.

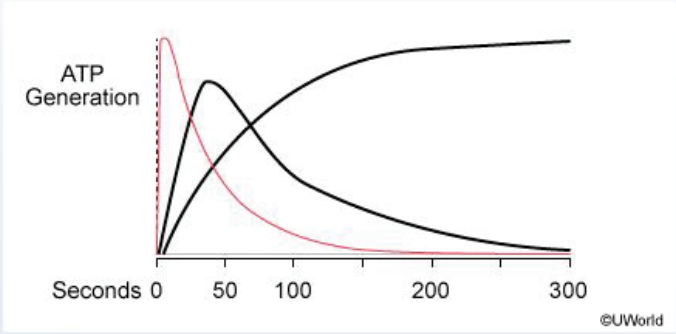
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- Phenotypic differences in mosaic Klinefelter patients as compared with non-mosaic Klinefelter patients.
- Clinical review: Klinefelter syndrome--a clinical update.

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A 24-year-old, healthy woman volunteers for an exercise research study. In the study, various radiolabeled compounds are used to determine the source of skeletal muscle ATP during exercise. The participants are given carbohydrate-rich food and are asked to run on a treadmill at high speed. Which of the following is the most likely source of ATP represented by the red curve on the graph below?

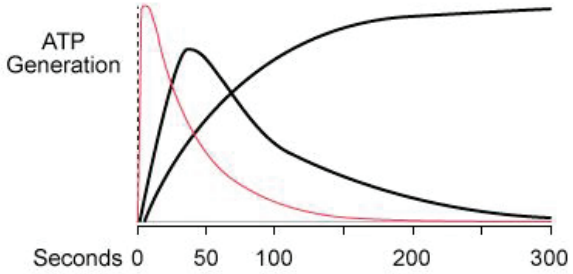


A. Amino acids
B. Free fatty acids
C. Glycogen
D. Ketone bodies

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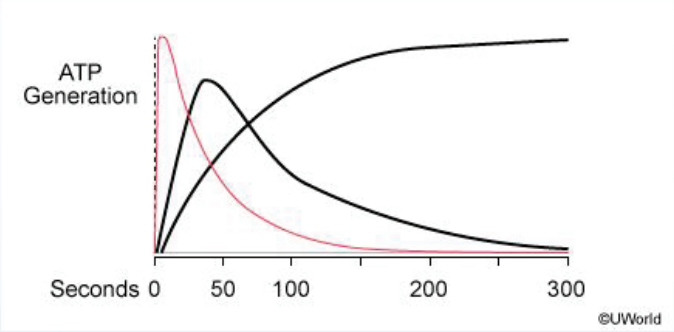


A. Amino acids
B. Free fatty acids
C. Glycogen
D. Ketone bodies
E. Phosphocreatine

Submit

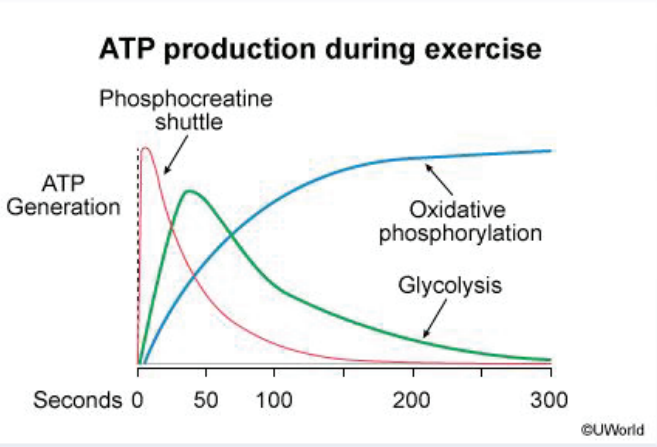
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the most likely source of ATP represented by the red curve on the graph below?



A. Amino acids (3%)
B. Free fatty acids (6%)
C. Glycogen (42%)
D. Ketone bodies (1%)
E. Phosphocreatine (45%)

45%
57 secs
11/08/2020



Skeletal muscle contraction requires the hydrolysis of ATP, which is only present in small amounts within the sarcoplasma. There are 3 main methods of **ATP production** during **intense exercise**, and the primary method varies with exercise duration.

The **phosphocreatine shuttle** is the primary source of ATP at the beginning (eg, **first 10 sec**) of exercise. As ATP is consumed by the muscle cell, creatine kinase removes inorganic phosphate molecules from phosphocreatine and combines them with ADP to regenerate ATP. Phosphocreatine supplies a brief burst of energy before being quickly depleted. Increased dietary intake of creatine can enhance this phase of

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As ATP is consumed by the muscle cell, creatine kinase removes inorganic phosphate molecules from phosphocreatine and combines them with ADP to regenerate ATP. Phosphocreatine supplies a brief burst of energy before being quickly depleted. Increased dietary intake of creatine can enhance this phase of ATP production by increasing sarcoplasmic phosphocreatine stores.

Once phosphocreatine is depleted, **anaerobic glycolysis** becomes the primary source of ATP for the next stage of exercise (eg, 10 to 60 sec). Muscle glycogen is rapidly broken down into glucose, which is converted to pyruvate (generating ATP in the process) and then lactic acid **(Choice C)**. However, the process quickly becomes limited by reduced sarcoplasmic pH caused by the accumulation of lactic acid.

Oxidative phosphorylation is the slowest of the 3 sources to reach peak production, but it is the most efficient generator of ATP and serves as the primary energy source for the remainder of exercise (eg, >60 sec). Pyruvate generated during glycolysis along with free fatty acids taken up from the circulation are converted to acetyl-coenzyme A, which is catabolized within the citric acid cycle (Krebs cycle) **(Choice B)**. This process produces NADH and $FADH_2$, which then enter the electron transport chain, where electrons are transferred to oxygen and large quantities of ATP are generated.

(Choices A and D) Amino acids and ketone bodies are sometimes used as an energy source for oxidative phosphorylation but only after glycogen and free fatty acid stores are depleted. Because amino acids are

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efficient generator of ATP and serves as the primary energy source for the remainder of exercise (eg, >60 sec). Pyruvate generated during glycolysis along with free fatty acids taken up from the circulation are converted to acetyl-coenzyme A, which is catabolized within the citric acid cycle (Krebs cycle) **(Choice B)**. This process produces NADH and $FADH_2$, which then enter the electron transport chain, where electrons are transferred to oxygen and large quantities of ATP are generated.

(Choices A and D) Amino acids and ketone bodies are sometimes used as an energy source for oxidative phosphorylation but only after glycogen and free fatty acid stores are depleted. Because amino acids are derived from muscle protein, their use as an energy source leads to muscle breakdown.

Educational objective:
Intense exercise creates a high demand for ATP, and the primary method of ATP production varies with the duration of exercise. The phosphocreatine shuttle is the primary source of ATP at the beginning of exercise, followed sequentially by anaerobic glycolysis and then oxidative phosphorylation.

Physiology	Endocrine, Diabetes & Metabolism	Physical exercise
Subject	System	Topic

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A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

A. ACTH
B. Growth hormone
C. Prolactin
D. Thyrotropin
E. Vasopressin

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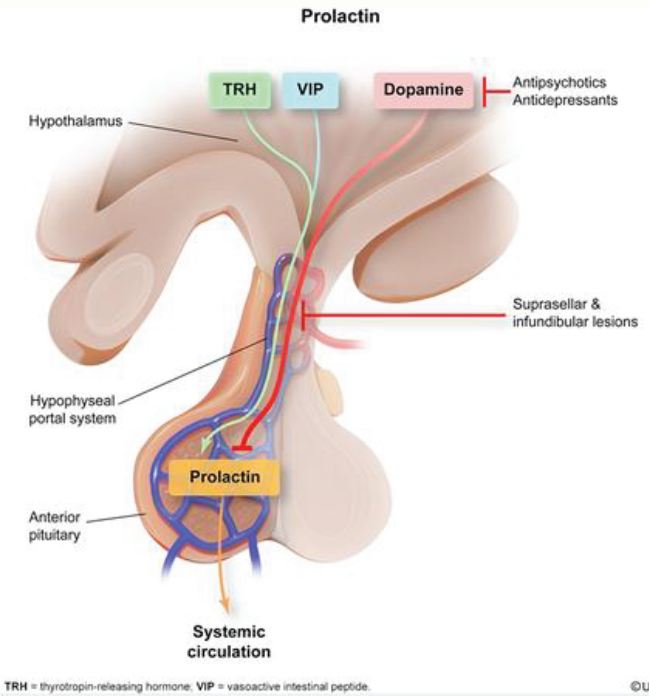
the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

A. ACTH (13%)
B. ~~Growth hormone~~ (3%)
C. Prolactin (67%)
D. ~~Thyrotropin~~ (6%)
E. ~~Vasopressin~~ (8%)

67%
02 mins, 52 secs
01/30/2021

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TRH = thyrotropin-releasing hormone; **VIP** = vasoactive intestinal peptide. ©UWorld

This patient with **sarcoidosis** has a hypothalamic and pituitary stalk mass with **mass-effect symptoms** (eg, headache, bitemporal visual field defects). In combination with the recurrent hypercalcemia (caused by excessive calcitriol formation by activated macrophages) 6 months after the discontinuation of glucocorticoid therapy, this presentation suggests active sarcoidosis with involvement of the hypothalamus (**neurosarcoidosis**). Although sarcoidosis classically causes noncaseating granulomas involving the lungs, lymph nodes, and skin, granulomas can form in any tissue.

Mass lesions in the hypothalamus or pituitary stalk can disrupt the hypothalamic-pituitary axis by obstructing the hypophyseal portal system. Unlike other pituitary hormones, **prolactin** release is **negatively regulated by dopamine** produced in the hypothalamus. Dopamine acts on the dopamine D2 receptors of lactotrophs, the prolactin-producing cells of the pituitary. Disruption of dopaminergic pathways (eg, by an infiltrating sarcoid lesion) in the pituitary stalk leads to **loss of inhibition** and a subsequent **increase in prolactin**.

(Choices A, B, and D) Pituitary adenomas can cause excess hormone formation; however, this patient has a hypothalamic mass, not a pituitary adenoma. In contrast to prolactin, other pituitary hormones (ACTH, growth hormone, thyrotropin [TSH], LH, and FSH) are inhibited by hypothalamic lesions because

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has a hypothalamic mass, not a pituitary adenoma. In contrast to prolactin, other pituitary hormones (ACTH, growth hormone, thyrotropin [TSH], LH, and FSH) are inhibited by hypothalamic lesions because the dominant effect of the hypothalamus on them is stimulatory. Although abruptly discontinuing an oral glucocorticoid can cause adrenal insufficiency with a subsequent increase in ACTH, low blood pressure, hypoglycemia, hyponatremia, and hyperkalemia would be expected. In addition, adrenal insufficiency typically occurs rapidly after glucocorticoid withdrawal (not 6 months later).

(Choice E) Vasopressin is produced in the supraoptic and paraventricular nuclei of the hypothalamus and transported to the posterior pituitary for release. Lesions of the hypothalamus and pituitary stalk can decrease vasopressin levels. Mass lesions in the central nervous system can cause vasopressin secretory dysregulation, leading to the syndrome of inappropriate antidiuretic hormone (SIADH) with euvolemic hyponatremia. However, the normal sodium levels in this patient exclude this syndrome.

Educational objective:
The release of prolactin is under inhibitory control by dopamine secretion from the hypothalamus. Disruption of dopaminergic pathways or blockade of dopamine D2 receptors can cause hyperprolactinemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperprolactinemia
Subject	System	Topic

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A 1-hour-old boy in the newborn nursery has jitteriness and irritability. His serum glucose is 21 mg/dL. The infant was born by cesarean delivery for macrosomia and failure to progress. The infant has not yet breastfed as his mother is still recovering from surgery. He weighs 4.5 kg (9 lb 15 oz). His mother was prescribed insulin for gestational diabetes but has not taken it regularly. She also has a history of depression and intravenous drug use. She denies use of illicit drugs during the pregnancy and tested negative for HIV and hepatitis B and C in her third trimester. Which of the following factors is the most likely cause of this neonate's hypoglycemia?

A. Beta cell hyperplasia
B. Glycogen storage disease
C. Hypothyroidism
D. Increased insulin-like growth factor 2 level
E. Placental transfer of insulin

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- A. Beta cell hyperplasia (70%)
- B. Glycogen storage disease (2%)
- C. Hypothyroidism (2%)
- D. Increased insulin-like growth factor 2 level (8%)
- E. Placental transfer of insulin (16%)

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Fetal effects of diabetes mellitus	
Embryopathy	• Congenital malformations* (eg, heart, neural tube defects)
Placental vasculopathy	• Asphyxia • Growth restriction • Polycythemia
Increased fetal insulin	• Macrosomia • Hypertrophic cardiomyopathy • Hypoglycemia after delivery

*Not common with gestational diabetes.

Poor glucose control before or during pregnancy is associated with adverse effects on the fetus and newborn. **Macrosomia** (>4 kg [8 lb 14 oz]) is a common finding in infants of diabetic mothers. Poor maternal glucose control leads to excessive **transplacental glucose** transfer to the fetus, which stimulates fetal insulin production. Chronic stimulation of the fetal beta cells leads to **beta cell hyperplasia** and **hyperinsulinism**. Elevated insulin levels contribute to increased fat deposition and enhanced fetal growth,

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hyperinsulinism. Elevated insulin levels contribute to increased fat deposition and enhanced fetal growth, resulting in macrosomia.

After delivery, the infant experiences a sudden interruption in transplacental glucose transfer, but the hyperinsulinism remains due to the beta cell hyperplasia. This can result in rapid development of profound **hypoglycemia**, and affected infants require frequent feedings or parenteral glucose to prevent hypoglycemia and subsequent neurologic injury. In most cases, supportive care is all that is required; the beta cell hyperplasia will resolve over time.

(Choice B) Glycogen storage diseases are caused by enzymatic defects that impair glycogenolysis. Types that affect the liver typically present with hypoglycemia and lactic acidosis. Symptoms usually do not start until age 3-4 months, when glycogenolysis is needed to sustain blood glucose during longer feeding intervals.

(Choice C) Most infants with hypothyroidism are asymptomatic. Clinical manifestations include lethargy, irritability, and poor feeding and growth. Hypoglycemia shortly after delivery is not a common finding in neonatal hypothyroidism.

(Choice D) Insulin-like growth factor 2 (IGF-2) is important in fetal development. However, IGF levels are not increased in infants of diabetic mothers.

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(Choice D) Insulin-like growth factor 2 (IGF-2) is important in fetal development. However, IGF levels are not increased in infants of diabetic mothers.

(Choice E) Maternal insulin is not transferred to the fetus but rather is catabolized by the placenta.

Educational objective:
Maternal hyperglycemia causes increased transplacental glucose delivery to the infant, fetal hyperglycemia, and, ultimately, beta cell hyperplasia. The resulting hyperinsulinemia caused by islet cell hyperplasia is associated with fetal macrosomia and hypoglycemia after delivery.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gestational diabetes
Subject	System	Topic

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A 6-month-old boy is brought to the office for a well-child visit. He is babbling, sitting with support, and rolling over. The patient is exclusively breastfed and has not yet started solid foods. The parents note that he has been straining while passing stool, which has been hard in consistency, over the last few weeks. The patient was diagnosed with congenital hypothyroidism based on newborn screening results, and levothyroxine was initiated at age 2 weeks. He also takes daily vitamin D and iron supplements. The patient has no other chronic medical conditions. Vital signs are normal for age. Weight gain is appropriate for age, but length has decreased from the 60th to the 40th percentile since the last visit. Physical examination is unremarkable. Thyroid function testing at age 4 months was normal. Results of routine follow-up laboratory testing are as follows:

TSH	8.0 μU/mL
Free thyroxine	0.3 ng/dL (normal: 0.5-2.3)

Which of the following is the most likely mechanism for this patient's abnormal thyroid function tests?

A. Decreased levothyroxine absorption

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Free thyroxine	0.3 ng/dL (normal: 0.5-2.3)

Which of the following is the most likely mechanism for this patient's abnormal thyroid function tests?

A. Decreased levothyroxine absorption
B. Decreased thyroxine-binding globulin
C. Excessive thyroid hormone supplementation
D. Inadequate dietary iodine
E. Thyroid hormone resistance

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examination is unremarkable. Thyroid function testing at age 4 months was normal. Results of routine follow-up laboratory testing are as follows:

TSH	8.0 µU/mL
Free thyroxine	0.3 ng/dL (normal: 0.5-2.3)

Which of the following is the most likely mechanism for this patient's abnormal thyroid function tests?

- A. Decreased levothyroxine absorption (47%)
- B. ~~Decreased thyroxine-binding globulin~~ (9%)
- C. ~~Excessive thyroid hormone supplementation~~ (5%)
- D. ~~Inadequate dietary iodine~~ (20%)
- E. Thyroid hormone resistance (16%)

Correct

47%

02 mins, 19 secs

09/21/2020

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Congenital hypothyroidism	
Clinical manifestations	• Asymptomatic at birth • After maternal thyroxine wanes (weeks to months): ◦ Lethargy, poor feeding ◦ Enlarged fontanelle ◦ Protruding tongue, puffy face, umbilical hernia ◦ Constipation ◦ Prolonged jaundice ◦ Dry skin
Diagnosis	• ↑ TSH & ↓ free thyroxine levels • Newborn screening
Treatment	• Levothyroxine*

*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

This patient with **treated congenital hypothyroidism** has **elevated TSH** and **low free thyroxine (T4)**, findings concerning for **ineffective therapy** with synthetic thyroid hormone (ie, levothyroxine). The most

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*Delayed treatment is associated with neurocognitive dysfunction (eg, ↓ intelligence quotient).

This patient with **treated congenital hypothyroidism** has **elevated TSH** and **low free thyroxine (T4)**, findings concerning for **ineffective therapy** with synthetic thyroid hormone (ie, levothyroxine). The most common cause of inadequate thyroid hormone levels in infants with treated congenital hypothyroidism is **rapid growth**, which increases the physiologic need for thyroid hormone. Another common reason for ineffective therapy is **decreased absorption of levothyroxine**.

Coadministration with various foods (eg, soy products) or drugs (eg, **iron**, **calcium, antacids**) can lead to poor intestinal absorption of levothyroxine. In this case, iron binding to levothyroxine in the gastrointestinal tract caused circulating levothyroxine levels to decrease, resulting in symptoms of hypothyroidism (eg, constipation, poor linear growth) and increased TSH production. Because this patient's thyroid function tests at age 4 months were normal, iron supplementation was likely started in the past 2 months to treat the physiologic waning of iron stores that occurs at this age.

(Choice B) Thyroxine-binding globulin (TBG) deficiency is characterized by low total T4 but normal TSH and free T4 levels. Patients do not require treatment because they are asymptomatic and euthyroid.

(Choice C) Excessive thyroid hormone supplementation would result in inhibition of TSH production and elevated T4 levels with signs of hyperthyroidism (eg, tachycardia, irritability, increased bowel movements).

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(Choice B) Thyroxine-binding globulin (TBG) deficiency is characterized by low total T4 but normal TSH and free T4 levels. Patients do not require treatment because they are asymptomatic and euthyroid.

(Choice C) Excessive thyroid hormone supplementation would result in inhibition of TSH production and elevated T4 levels with signs of hyperthyroidism (eg, tachycardia, irritability, increased bowel movements).

(Choice D) Deficiency of iodine, which is required for thyroid hormone synthesis, rarely causes hypothyroidism in resource-rich countries due to dietary iodine found in salt. Breast milk also provides adequate iodine for infants, making this diagnosis unlikely.

(Choice E) Thyroid hormone resistance is caused by thyroid hormone receptor mutations and results in elevated TSH and T4 levels due to impaired feedback inhibition. Signs of hypothyroidism or hyperthyroidism can occur due to varying tissue sensitivity to thyroid hormones.

Educational objective:
Coadministration of levothyroxine with various foods (eg, soy products) and certain medications (eg, iron, calcium, antacids) can lead to poor intestinal absorption of levothyroxine and symptoms of hypothyroidism while on therapy.

References

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A 6-year-old Caucasian girl is brought to your office by her mother. The mother says that her daughter is "womanly," including being exceptionally tall for her age. Physical examination reveals Tanner Stage 3 breast development and coarse pubic hair. The child's height is in the 96th percentile. You explain to her mother that, although this girl is very tall now, she will ultimately be shorter than average if she does not get treatment. Which of the following is the physiologic explanation for the information you provided?

A. Estrogen effect on the long bone diaphysis
B. Estrogen effect on the long bone epiphysis
C. Estrogen effect on the long bone epiphyseal plate
D. Somatomedin C effect on the long bone diaphysis
E. Somatomedin C effect on the long bone epiphyseal plate

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A. Estrogen effect on the long bone diaphysis (2%)
B. Estrogen effect on the long bone epiphysis (6%)
C. Estrogen effect on the long bone epiphyseal plate (77%)
D. Somatomedin C effect on the long bone diaphysis (1%)
E. Somatomedin C effect on the long bone epiphyseal plate (11%)

Correct

77% Answered correctly

52 secs Time Spent

01/09/2021 Last Updated

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The child described in the vignette is six years old and has already undergone pubertal changes, as indicated by her Tanner staging. (Also called the sexual maturity rating, Tanner staging is a systematic, universalized method that uses female breast and pubic hair development to categorize development.) Precocious puberty in Caucasian females is defined as the development of secondary sexual characters at an age less than seven years.

Young bone has several layers; their order from middle to end is diaphysis, metaphysis, epiphyseal cartilage, and epiphysis. The epiphyseal cartilage, also called the "growth plate, is responsible for linear growth.

Linear growth stops when the epiphyseal growth plate closes, i.e. when the epiphysis fuses with the metaphysis. Sex steroids initially increase linear growth, but they also encourage closure of epiphyseal growth plates. Once the growth plates have closed, linear growth is irreversibly stopped. In normal puberty, there is a rapid increase in growth. At the end of this pubertal growth spurt, almost 90% of the final height is achieved. Although this child is currently taller than her peers, the excess steroids will soon cause epiphyseal growth plate closure; hence, if this patient is not treated, she will ultimately not meet her full growth potential.

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(Choices A and B) In sites other than the epiphyseal growth plate, the effect of estrogen on bone is anabolic because estrogen increases osteoblastic bone deposition and decreases osteoclastic bone resorption. Low estrogenic states, such as menopause, are associated with rapid bone loss.

(Choices D and E) The secretion of somatomedin C, more commonly known as insulin-like growth factor-1 (IGF-1), is directly increased when growth hormone is secreted from the pituitary gland. IGF-1 causes the differentiation and proliferation of chondrocytes in the epiphyseal growth plate, causing an increase in linear growth. However, unlike estrogen, IGF-1 does not accelerate epiphyseal closure.

Educational Objective:

Sex hormones promote both growth and epiphyseal plate closure; hence, precocious puberty may result in a shorter stature, despite an initial growth spurt. Gigantism is caused by excessive pituitary production of growth hormone; these patients achieve enormous heights because, unlike excessive sex steroids, excessive IGF-1 does not lead to premature closure of the epiphysis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Precocious puberty
Subject	System	Topic

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A 65-year-old woman comes to the emergency department due to left leg pain and swelling for the past day. She has had no trauma or fever. The patient has a history of hypertension, congestive heart failure, type 2 diabetes mellitus, and osteoporosis. Family history is notable for breast cancer in her mother and sister. She takes multiple medications. Temperature is 37.8 C (100 F), blood pressure is 130/80 mm Hg, and pulse is 99/min. Pulse oximetry shows 98% on ambient air. The lungs are clear to auscultation, and heart sounds are normal without murmur. There is tenderness and edema of the left lower extremity up to the mid thigh. Venous Doppler ultrasonography reveals an occluding thrombus in the left femoral and popliteal veins. Which of the following pharmacotherapies most likely contributed to this patient's current condition?

A. Alendronate
B. Chlorthalidone
C. Empagliflozin
D. Liraglutide
E. Raloxifene

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- A. Alendronate
- B. Chlorthalidone
- C. Empagliflozin
- D. Liraglutide
- E. Raloxifene
- F. Sacubitril-valsartan
- G. Spironolactone

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A. Alendronate (7%)
B. Chlorthalidone (6%)
C. Empagliflozin (2%)
D. Liraglutide (2%)
✓ E. Raloxifene (72%)
F. Sacubitril-valsartan (3%)
G. Spironolactone (4%)

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Explanation

Selective estrogen receptor modulators	
Drugs	• Tamoxifen • Raloxifene
Mechanism of action	• Competitive inhibitor of estrogen binding • Mixed agonist/antagonist action
Indications	• Prevention of breast cancer in high-risk patients • Tamoxifen: adjuvant treatment of breast cancer • Raloxifene: postmenopausal osteoporosis
Adverse effects	• Hot flashes • Venous thromboembolism • Endometrial hyperplasia & carcinoma (tamoxifen only)

Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, are nonsteroidal compounds that bind to estrogen receptors and exhibit estrogen antagonist and agonist properties in a

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Selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, are nonsteroidal compounds that bind to estrogen receptors and exhibit estrogen antagonist and agonist properties in a tissue-specific manner. **Raloxifene** has estrogen agonist activity on bone, inhibiting bone resorption and improving bone mineral density while exhibiting estrogen antagonist activity in the breast and endometrial tissue.

Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, cause a prothrombotic state and can increase the risk for **venous thromboembolism** (VTE). Proposed mechanisms include increased levels of clotting factors (eg, prothrombin; fibrinogen; factor VII, VIII, X) and activated protein C resistance. Current or prior thromboembolic disorders are contraindications to SERM use.

(Choice A) Bisphosphonates (eg, alendronate) inhibit osteoclast-mediated bone resorption. Side effects include hypocalcemia, esophagitis, and osteonecrosis of the jaw. Bisphosphonates have no estrogenic activity and do not increase the risk for VTE.

(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule, decreasing reabsorption of Na^+ and increasing reabsorption of calcium, which can be beneficial in patients with osteoporosis. Side effects include electrolyte abnormalities, hyperglycemia, and

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(Choice B) Thiazide diuretics (eg, chlorthalidone) inhibit Na^+/Cl^- cotransporters in the distal convoluted tubule, decreasing reabsorption of Na^+ and increasing reabsorption of calcium, which can be beneficial in patients with osteoporosis. Side effects include electrolyte abnormalities, hyperglycemia, and hyperlipidemia.

(Choice C) Sodium-glucose cotransporter 2 inhibitors (eg, empagliflozin) reduce reabsorption of glucose in the proximal renal tubule, leading to urinary glucose excretion. Side effects include urinary tract and genital mycotic infections as well as hypotension.

(Choice D) Glucagon-like peptide-1 (GLP-1) is released by the small intestine in response to food and induces glucose-dependent insulin release from pancreatic beta cells. GLP-1 agonists (eg, liraglutide) lower blood glucose with little hypoglycemia risk, but can cause gastrointestinal upset and weight loss.

(Choice F) Sacubitril is a neprilysin inhibitor that increases atrial natriuretic peptide and brain natriuretic peptide levels (thereby promoting diuresis and vasodilation) in patients with heart failure. It is administered with an angiotensin II receptor blocker (valsartan) to offset the associated increase in angiotensin II levels. Side effects include cough, hyperkalemia, and renal impairment.

(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed

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(Choice G) Spironolactone is an aldosterone antagonist used in patients with heart failure. It has prominent anti-androgenic effects, which can lead to gynecomastia in male patients due to unopposed estrogenic effects on breast tissue. However, it has minimal effects on estrogen levels and does not increase the risk of VTE.

Educational objective:
Raloxifene is a selective estrogen receptor modulator (SERM) that has estrogen agonist activity on bone and decreases bone resorption. Medicines with estrogen agonist activity, including SERMs, oral contraceptives, and hormone replacement therapy, can increase the risk for venous thromboembolism.

References

- Selective estrogen receptor modulators in menopause

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A 46-year-old woman comes to the office due to episodes of headaches, nausea, sweating, and feeling like she is going to pass out. The patient has had 3 such episodes in the past 2 weeks, with symptoms occurring when she skips a meal. During the most recent episode, her fingerstick glucose was 50 mg/dL. She was diagnosed with type 2 diabetes mellitus 3 years ago and was initially treated with metformin monotherapy; glyburide was added to her regimen 3 months ago due to inadequate glycemic control. The patient has no other medical conditions. Vital signs are within normal limits, and physical examination shows no abnormalities. Laboratory results show hemoglobin A1c is 6.7%. The medication most likely causing this patient's current symptoms works by targeting which of the following?

A. Intracellular mitochondrial enzymes
B. Intracellular nuclear receptors
C. Membrane ion channels
D. Surface adenylate cyclase–coupled receptors
E. Surface membrane-bound enzymes
F. Surface tyrosine kinase receptor

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occurring when she skips a meal. During the most recent episode, her fingerstick glucose was 50 mg/dL. She was diagnosed with type 2 diabetes mellitus 3 years ago and was initially treated with metformin monotherapy; glyburide was added to her regimen 3 months ago due to inadequate glycemic control. The patient has no other medical conditions. Vital signs are within normal limits, and physical examination shows no abnormalities. Laboratory results show hemoglobin A1c is 6.7%. The medication most likely causing this patient's current symptoms works by targeting which of the following?

A. Intracellular mitochondrial enzymes (2%)
B. Intracellular nuclear receptors (4%)
C. Membrane ion channels (74%)
D. Surface adenylate cyclase–coupled receptors (5%)
E. Surface membrane-bound enzymes (2%)
F. Surface tyrosine kinase receptor (10%)

Correct

74%

56 secs

10/26/2020

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Noninsulin antidiabetic agents for type 2 diabetes mellitus		
Agent	**Mechanism of action**	**Side effects**
Insulin secretagogues • Sulfonylureas • Meglitinides	↑ Insulin secretion by inhibiting β-cell K_{ATP} channels	• Hypoglycemia • Weight gain
Biguanides • Metformin	Stimulate AMPK & inhibit mitochondrial gluconeogenesis, ↓ hepatic glucose production & ↑ peripheral glucose uptake	• Diarrhea • Lactic acidosis
Thiazolidinediones • Pioglitazone	Activate transcription regulator PPAR-γ, ↓ insulin resistance	• Fluid retention/heart failure • Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss

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		• Weight gain
GLP-1 agonists • Exenatide • Liraglutide	↑ Glucose-dependent insulin secretion, ↓ glucagon secretion, delayed gastric emptying	• Pancreatitis • Weight loss
DPP4 inhibitors • Sitagliptin • Saxagliptin	↑ Endogenous GLP-1 & GIP levels	• Nasopharyngitis
α-glucosidase inhibitors • Acarbose • Miglitol	↓ Intestinal disaccharide absorption	• Diarrhea • Flatulence
SGLT2 inhibitors • Canagliflozin • Dapagliflozin	↑ Renal glucose excretion	• Urinary tract infections • Hypotension

AMPK = adenosine monophosphate–activated protein kinase; **DPP4** = dipeptidyl peptidase-4; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagonlike peptide-1; **K_{ATP}** = ATP-sensitive potassium;

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This patient has symptomatic hypoglycemia following initiation of a sulfonylurea medication (ie, glyburide) for diabetes mellitus. **Sulfonylureas** inhibit the **ATP-sensitive potassium channel** on the pancreatic beta **cell membrane**, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell **insulin release** independent of blood glucose concentrations.

Sulfonylureas continue to stimulate insulin secretion even when blood glucose levels are normal, which can lead to hypoglycemia. The longer-acting sulfonylureas (eg, glyburide) are more prone to causing **hypoglycemia** than shorter-acting drugs (eg, glipizide). Meglitinides (eg, repaglinide, nateglinide) are short-acting drugs that are functionally similar to sulfonylureas.

(Choice A) Metformin inhibits the mitochondrial enzymes required for gluconeogenesis, leading to decreased hepatic glucose production and lower circulating glucose levels. It also increases peripheral glucose uptake and improves insulin sensitivity by activating AMP-activated protein kinase. Metformin does not increase endogenous insulin secretion and is therefore less likely to cause hypoglycemia than sulfonylureas.

(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism

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(Choice B) Thiazolidinediones (eg, pioglitazone) decrease insulin resistance by binding to peroxisome proliferator–activated receptor gamma, a transcriptional regulator of genes involved in glucose and lipid metabolism.

(Choice D) Glucagon-like polypeptide-1 (GLP-1) is secreted by intestinal L cells in response to food intake, and regulates glucose by slowing gastric emptying and increasing insulin release. GLP-1 (and pharmacologic GLP-1 agonists such as exenatide) acts through cell surface receptors that are coupled with a G protein–adenylyl cyclase system.

(Choice E) Alpha-glucosidase inhibitors (eg, acarbose, miglitol) decrease the activity of disaccharidases on the intestinal brush border. Because carbohydrates are absorbed as monosaccharides, the inhibition of disaccharide breakdown delays carbohydrate absorption.

(Choice F) Insulin acts by binding to a cell surface receptor consisting of 2 alpha and 2 beta subunits. The alpha subunits are located extracellularly and provide binding sites for insulin. The membrane-spanning beta subunits contain the intracellular tyrosine kinase domains.

Educational objective:
Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin

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(Choice F) Insulin acts by binding to a cell surface receptor consisting of 2 alpha and 2 beta subunits. The alpha subunits are located extracellularly and provide binding sites for insulin. The membrane-spanning beta subunits contain the intracellular tyrosine kinase domains.

Educational objective:

Sulfonylureas inhibit the ATP-sensitive potassium channel on the pancreatic beta cell membrane, inducing depolarization and L-type calcium channel opening. The increased Ca^{2+} influx stimulates beta cell insulin release independent of blood glucose concentrations. Sulfonylureas can induce hypoglycemia because they stimulate insulin secretion even when blood glucose levels are normal.

References

- The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes

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A 34-year-old man comes to the office due to a 6-month history of progressively worsening headaches. He has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone
A.	↓	↓	↓
B.	↑	↓	↓
C.	↑	↑	↓
D.	↑	↑	↑
E.	↓	↓	↑

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has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone	
✓ A.	↓	↓	↓	(68%)
B.	↑	↓	↓	(18%)
C.	↑	↑	↓	(4%)
D.	↑	↑	↑	(4%)
E.	↓	↓	↑	(3%)

Correct

68%

55 secs

01/13/2021

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Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism)

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(LH, FSH)	(hypopituitarism) • Mass effect

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial imaging (typically MRI scan) can confirm the diagnosis of a pituitary adenoma. Unlike other pituitary hormones, prolactin secretion is under negative regulation by dopamine from the hypothalamus, and any disruption of dopaminergic pathways in the pituitary stalk can cause a moderate increase in prolactin release. However, **very high prolactin levels**, as seen in this patient, suggest a prolactin-secreting adenoma (**prolactinoma**).

Increased circulating levels of prolactin suppress GnRH secretion, leading to a reduction in release of LH from the pituitary and decreased testicular testosterone production. In premenopausal women, prolactinomas typically present early with galactorrhea and amenorrhea. However, in men and postmenopausal women, early symptoms may be subtle and nonspecific (eg, decreased libido), and patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH, FSH) and subsequently testosterone secretion. However, prolonged, continuous GnRH secretion suppresses gonadotropins, resulting in lower levels of sex steroids. Long-acting GnRH agonists (eg, leuprolide) are used to suppress sex steroid–dependent diseases (eg, prostate cancer)

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patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH, FSH) and subsequently testosterone secretion. However, prolonged, continuous GnRH secretion suppresses gonadotropins, resulting in lower levels of sex steroids. Long-acting GnRH agonists (eg, leuprolide) are used to suppress sex steroid–dependent diseases (eg, prostate cancer).

(Choice C) Primary hypogonadism with low testosterone levels results in loss of negative feedback on GnRH release, causing elevated levels of GnRH and LH.

(Choice E) Intake of exogenous testosterone (eg, anabolic steroid use) will suppress release of GnRH and subsequently LH.

Educational objective:
Large prolactin-secreting pituitary tumors can compress the optic chiasm, causing bitemporal hemianopsia. In addition, elevated prolactin levels suppress release of GnRH, leading to decreased LH secretion and subsequently impaired testosterone production in men.

References

- Pituitary adenomas: an overview.

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A 40-year-old man comes to the office due to erectile dysfunction and loss of libido. The patient's history is notable for Hodgkin lymphoma that was treated with chemotherapy. Physical examination is normal except for small testes. Laboratory evaluation shows consistently low total and free early morning testosterone levels and elevated serum LH. Transdermal testosterone therapy is prescribed. Which of the following should be periodically monitored during this patient's treatment?

- A. ECG
- B. Hematocrit
- C. Serum cortisol
- D. Serum creatinine
- E. Serum TSH and thyroxine

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A. ECG (5%)
B. Hematocrit (48%)
C. Serum cortisol (22%)
D. Serum creatinine (6%)
E. Serum TSH and thyroxine (16%)

Correct

48%
Answered correctly

15 secs
Time Spent

11/06/2020
Last Updated

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Testosterone replacement therapy	
Indications	• Symptoms of hypogonadism • Consistently low serum testosterone
Contraindications	• Prostate cancer (elevated PSA) • Hematocrit >50% • Severe obstructive sleep apnea
Adverse effects	• Erythrocytosis • Venous thromboembolism

PSA = prostate-specific antigen.

This patient has **hypogonadism** presenting with erectile dysfunction and loss of libido associated with a low serum testosterone level. Other common manifestations of hypogonadism include fatigue, loss of muscle mass, and decreased bone density. Hypogonadism is a common complication of cytotoxic chemotherapy (eg, cyclophosphamide) in long-term cancer survivors. **Testosterone replacement therapy** (TRT) is indicated for men with symptoms of hypogonadism and persistently low serum testosterone levels.

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muscle mass, and decreased bone density. Hypogonadism is a common complication of cytotoxic chemotherapy (eg, cyclophosphamide) in long-term cancer survivors. **Testosterone replacement therapy** (TRT) is indicated for men with symptoms of hypogonadism and persistently low serum testosterone levels.

However, testosterone has trophic effects on the prostate, mediated by conversion to dihydrotestosterone by 5-alpha reductase in local tissues. TRT is associated with increased prostate volume, a rise in serum **prostate-specific antigen** (PSA), and a possible increase in the risk for prostate cancer. PSA should be measured prior to initiation of therapy and periodically thereafter.

In addition, TRT can induce **erythrocytosis**, possibly due to suppression of hepcidin and increased intestinal iron absorption. This can lead to increased blood viscosity and an elevated risk for thromboembolism. Therefore, TRT should not be initiated in patients with a baseline hematocrit >50%, and **hematocrit** should be followed regularly during treatment.

(Choice A) Some experts believe there is an increased risk of cardiovascular events associated with TRT and patients should be advised of this possibility. However, testing (eg, ECG) in asymptomatic patients is not necessary.

(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested for deficiencies in other hypothalamic-pituitary systems (eg,

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hematocrit should be followed regularly during treatment.

(Choice A) Some experts believe there is an increased risk of cardiovascular events associated with TRT and patients should be advised of this possibility. However, testing (eg, ECG) in asymptomatic patients is not necessary.

(Choices C and E) Patients with central/secondary hypogonadism (ie, low testosterone with low or inappropriately normal LH) should be tested for deficiencies in other hypothalamic-pituitary systems (eg, TSH + serum thyroxine, morning cortisol). However, this patient has an elevated LH level consistent with primary hypogonadism, making these additional tests unnecessary.

(Choice D) Because renal toxicity is not a major concern with TRT, renal function does not need to be monitored.

Educational objective:
Testosterone replacement therapy is indicated for men with symptomatic hypogonadism. It is associated with an increase in serum prostate-specific antigen and may raise the risk of prostate cancer. In addition, testosterone therapy can cause erythrocytosis (leading to thromboembolism), and hematocrit should be regularly monitored.

References

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A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

A. Glycogen phosphorylase
B. Hormone-sensitive lipase
C. Lipoprotein lipase
D. Mitochondrial HMG CoA synthase
E. Phosphofructokinase-1

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past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

A. ~~Glycogen phosphorylase~~ (17%)

✓ B. Hormone-sensitive lipase (40%)

C. Lipoprotein lipase (11%)

D. Mitochondrial HMG CoA synthase (20%)

E. Phosphofructokinase-1 (10%)

Correct

40%

01 min, 32 secs

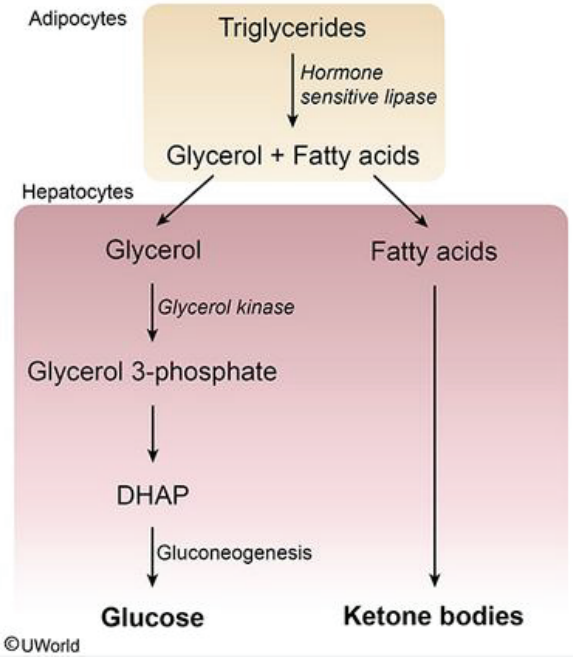
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Exhibit Display

Triglyceride metabolism during fasting



Zoom In | Zoom Out | Reset | New | Existing | My Notebook

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This patient's laboratory studies show the presence of ketones in the urine and maintenance of fasting blood glucose values in the low-normal range despite prolonged fasting.

Hormone-sensitive lipase (HSL) is an enzyme found in adipose tissue that catalyzes the mobilization of stored triglycerides into **free fatty acids** (FFAs) and **glycerol**. HSL is activated in response to stress hormones (eg, catecholamines, glucagon, ACTH), whereas it is inhibited by the release of insulin. The stress hormones stimulate Gs protein-coupled receptors on adipocytes, leading to increased cAMP production and activation of protein kinase A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carbon source for **gluconeogenesis**. The liver oxidizes the FFAs to acetyl-coA, which can then be further metabolized to **ketone bodies** (eg, acetoacetate, beta-hydroxybutyrate) or shunted into the TCA cycle to generate energy for gluconeogenesis. During starvation, most tissues utilize a combination of FFAs and ketones for their energy needs. Important exceptions include the brain (FFAs do not cross the blood-brain barrier, so only ketone bodies/glucose can be used) and erythrocytes (can use only glucose due to lack of mitochondria).

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(Choice A) Glycogen phosphorylase is the rate-limiting enzyme in glycogenolysis, a process that frees glucose-1-phosphate from stored glycogen chains. Glycogenolysis increases blood glucose levels during the first several hours of fasting but has no effect on fatty acid oxidation.

(Choice C) Lipoprotein lipase is an enzyme found on endothelial cells that functions to degrade triglycerides found in chylomicrons and VLDL. Although it is functionally similar to HSL, it works in the bloodstream to form FFAs that are then transported into adipocytes storage or used by tissues (eg, heart/skeletal muscle) for energy production.

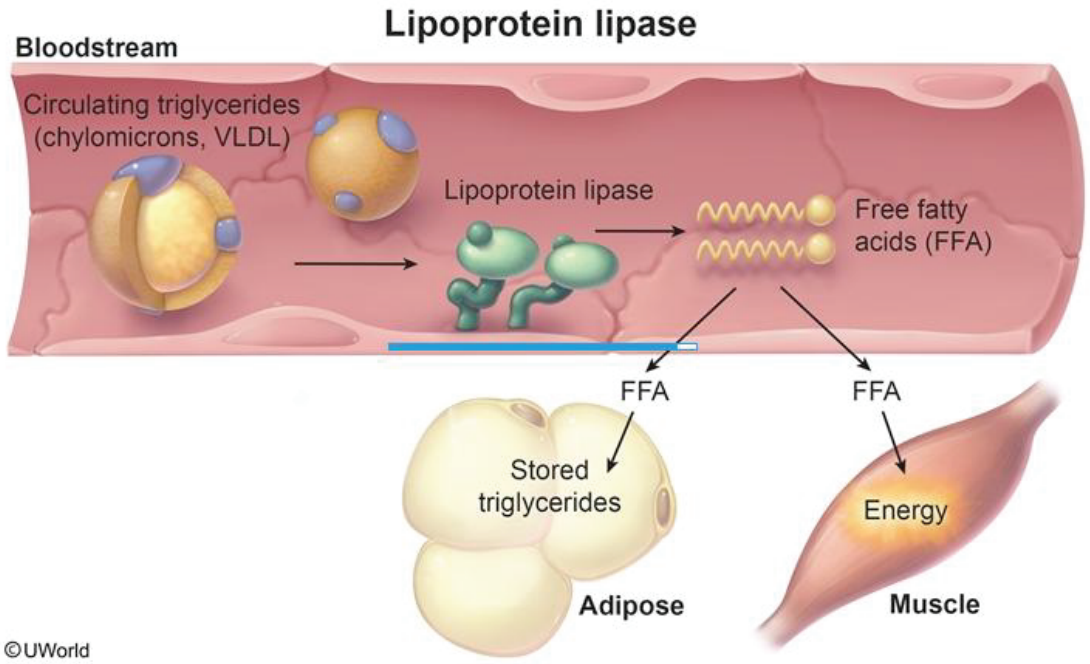
(Choice D) Mitochondrial HMG-CoA synthase plays a role in the production of ketones. Although it could be responsible for the presence of urinary ketone bodies in this patient, it would not account for the maintenance of blood glucose levels.

(Choice E) Phosphofructokinase-1 catalyzes the major rate-limiting step in glycolysis by converting fructose-6-phosphate to fructose-1,6-bisphosphate. It is not involved in gluconeogenesis or ketone production.

Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates

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Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatic gluconeogenesis and ketone body formation.

References

- Lipolysis: more than just a lipase.

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A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no medications and has no other medical problems. After the initial laboratory workup, an abdominal CT is performed that shows a 2-cm left-sided adrenal mass. The patient undergoes an uncomplicated left-sided adrenalectomy. Gross examination of the adrenal gland demonstrates a well-defined yellowish tumor within the cortex. Assuming the tumor cells are functionally similar to cells from the outermost layer of the adrenal cortex, this patient would most likely have presented with which of the following additional symptoms?

A. Diarrhea and flushing
B. Excessive hair growth
C. Paresthesias and muscle weakness
D. Sweating and tremulousness
E. Weight gain and easy bruising

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A. Diarrhea and flushing (6%)
B. Excessive hair growth (5%)
✓ C. Paresthesias and muscle weakness (58%)
D. Sweating and tremulousness (13%)
E. Weight gain and easy bruising (15%)

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Explanation

Primary hyperaldosteronism	
Etiology	• Bilateral adrenal hyperplasia (60%) • Unilateral adrenal adenoma
Clinical features	• **Hypertension** • **Hypokalemic alkalosis**: Muscle weakness & paresthesias
Diagnosis	• **Elevated plasma aldosterone** • **Low plasma renin activity** • Aldosterone remains elevated following oral saline load

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Presumably, this patient had symptoms of **primary hyperaldosteronism** due to an **aldosterone-producing adenoma** (Conn syndrome). Adrenocortical adenomas appear as well-defined yellowish tumors of the adrenal cortex on gross examination, regardless of functional status. This tumor is functionally similar to the outermost layer of the adrenal cortex, which normally produces aldosterone

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Presumably, this patient had symptoms of **primary hyperaldosteronism** due to an **aldosterone-producing adenoma** (Conn syndrome). Adrenocortical adenomas appear as well-defined yellowish tumors of the adrenal cortex on gross examination, regardless of functional status. This tumor is functionally similar to the outermost layer of the adrenal cortex, which normally produces aldosterone.

Aldosterone acts on renal cortical collecting ducts to facilitate the exchange of Na^+ for K^+ and H^+ in the tubular fluid. As a result, excess production of aldosterone causes renal Na^+ retention and excess urinary K^+ and H^+ secretion, resulting in hypertension, hypokalemia, and metabolic alkalosis. These electrolyte abnormalities can cause **paresthesias** and **muscle weakness** in some patients with primary hyperaldosteronism. Significant extracellular fluid volume expansion does not occur in primary hyperaldosteronism due to aldosterone escape.

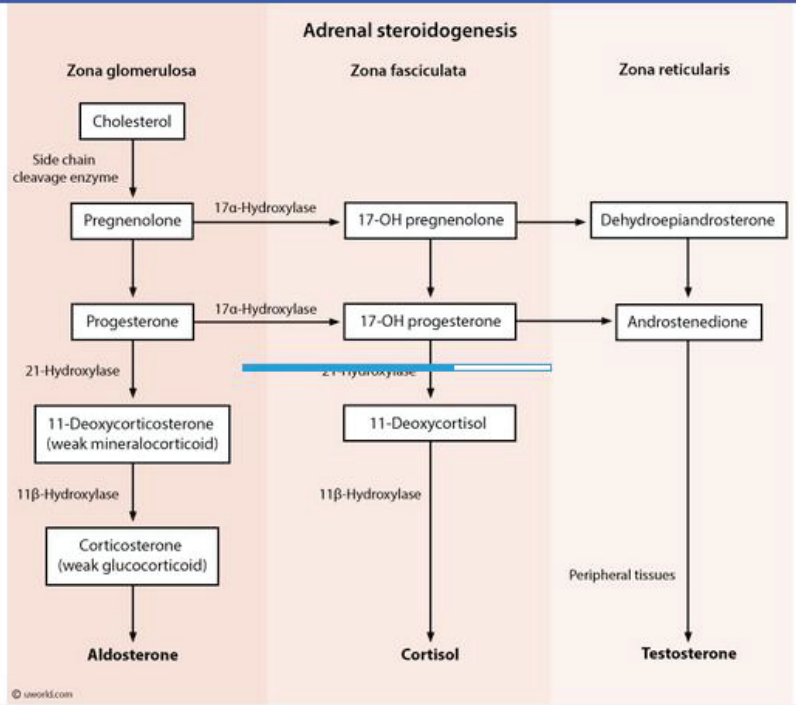
(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the third (innermost) layer of the adrenal cortex, the zona reticularis.

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adrenal cortex: the zona reticularis.

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(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the third (innermost) layer of the adrenal cortex, the zona reticularis.

(Choice D) Sweating and tremulousness can be caused by excess circulating catecholamines, which may result from a pheochromocytoma. These tumors arise from the adrenal medulla rather than the adrenal cortex.

(Choice E) Patients with Cushing syndrome often develop weight gain due to central fat accumulation, along with easy bruising and weakening of the skin and subcutaneous connective tissue. Cortisol-secreting adrenal lesions would be functionally similar to the middle layer of the adrenal cortex (zona fasciculata).

Educational objective:
Hypersecreting adrenocortical tumors can have functionality resembling the outer (aldosterone/Conn syndrome), middle (cortisol/Cushing syndrome), or inner (androgens/hirsutism and virilization) layers of the adrenal cortex.

References

- Diagnosis and management of primary aldosteronism: an updated review.

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A 45-year-old woman is evaluated 2 weeks after she fractured her left radius during a fall from standing height. Two months previously, she passed a renal stone. There is no family history of osteoporosis or hypercalcemia. Physical examination is unremarkable. Serum laboratory results are as follows:

Calcium	11.3 mg/dL
Phosphorus	2.4 mg/dL
Creatinine	1.0 mg/dL
Albumin	4.1 g/dL
Parathyroid hormone	75 pg/mL (normal: 10-65)

Bone density testing performed using dual-energy x-ray absorptiometry reveals osteoporosis. Which of the following is the major contributor to bone loss in this patient?

A. Decreased bone formation due to decreased conversion of calcidiol to calcitriol

B. Decreased bone formation due to excessive loss of calcium in urine

C. Decreased bone formation due to inhibition of osteoblast differentiation

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Phosphorus	2.4 mg/dL
Creatinine	1.0 mg/dL
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B. Decreased bone formation due to excessive loss of calcium in urine
C. Decreased bone formation due to inhibition of osteoblast differentiation
D. Increased bone resorption due to decreased intestinal calcium absorption
E. Increased bone resorption due to paracrine stimulation of osteoclasts

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Phosphorus	2.4 mg/dL
Creatinine	1.0 mg/dL
Albumin	4.1 g/dL
Parathyroid hormone	75 pg/mL (normal: 10-65)

Bone density testing performed using dual-energy x-ray absorptiometry reveals osteoporosis. Which of the following is the major contributor to bone loss in this patient?

A. Decreased bone formation due to decreased conversion of calcidiol to calcitriol (2%)
B. Decreased bone formation due to excessive loss of calcium in urine (5%)
C. Decreased bone formation due to inhibition of osteoblast differentiation (7%)
D. Increased bone resorption due to decreased intestinal calcium absorption (6%)
✓ E. Increased bone resorption due to paracrine stimulation of osteoclasts (78%)

Correct

78%
Answered correctly

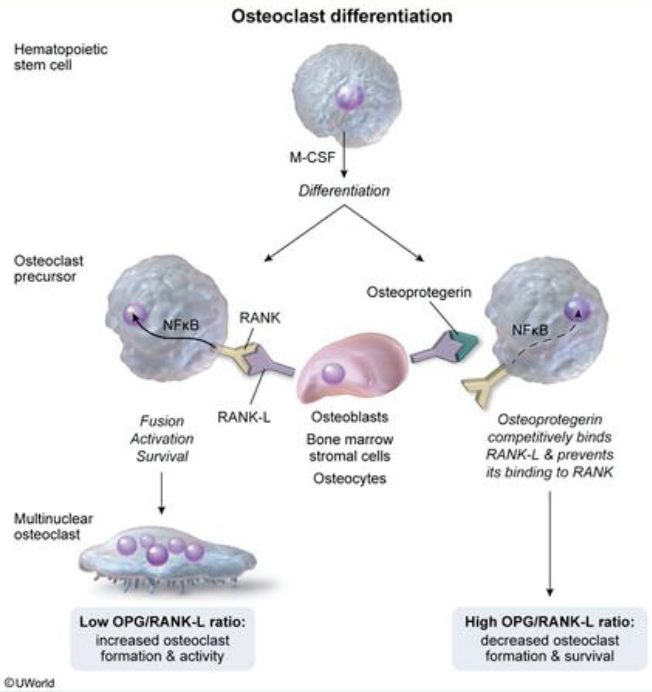
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Activation Bone marrow competitively binds

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This patient has hyperparathyroidism, presenting with **osteoporosis** and nephrolithiasis associated with mild **hypercalcemia** and an inappropriately **elevated parathyroid hormone** (PTH) level.

PTH increases bone turnover by stimulating the differentiation and activity of osteoblasts, leading to increased bone formation. In addition, PTH upregulates the expression of receptor activator of nuclear factor kappa B ligand (RANK-L) on the surface of the activated osteoblasts, which binds RANK on nearby osteoclast precursor cells and induces maturation to active osteoclasts. Therefore, **PTH** causes **bone formation** (by direct effect on osteoblasts) and **bone resorption** (by paracrine effect on osteoclasts). Bone turnover is normally **balanced**, with bone formation proportionate to resorption.

In **hyperparathyroid states**, continuous exposure to high PTH levels cause increased RANK-L expression along with suppression of osteoprotegerin (a counterregulatory decoy receptor). This leads to greater bone resorption than formation and **net bone loss**.

(Choices A and D) PTH upregulates 1-alpha-hydroxylase in the kidneys, which leads to increased (not decreased) conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol subsequently induces increased (not decreased) intestinal calcium absorption.

(Choice B) PTH increases renal reabsorption of calcium. Despite this, hypercalciuria is common in

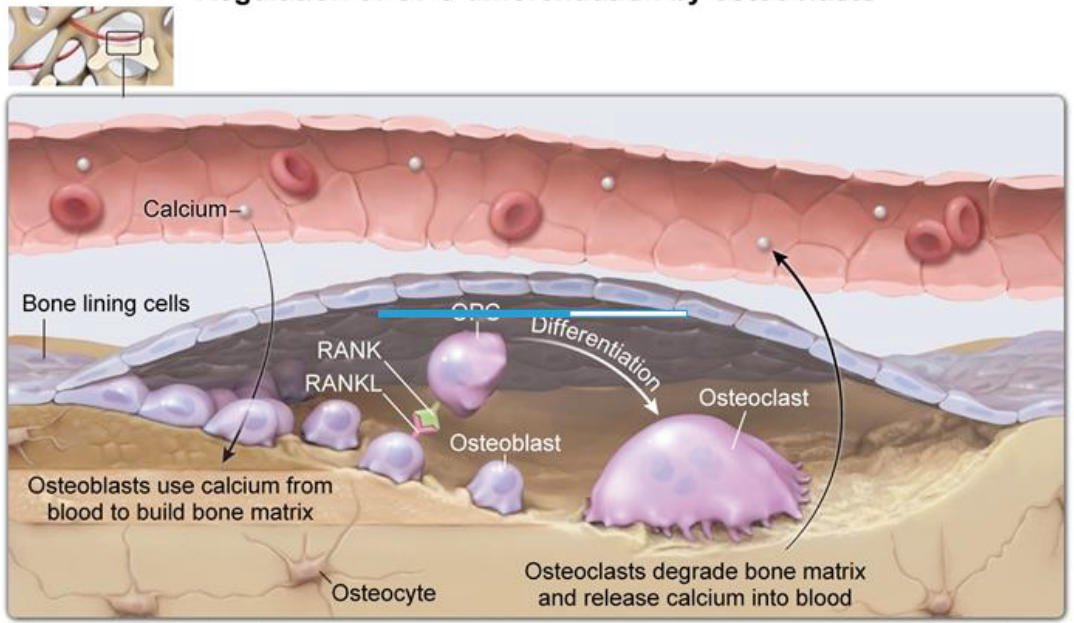
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Regulation of OPC differentiation by osteoblasts



OPC = osteoclast progenitor cell.

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subsequently induces increased (not decreased) intestinal calcium absorption.

(Choice B) PTH increases renal reabsorption of calcium. Despite this, hypercalciuria is common in hyperparathyroidism because the filtered calcium load may exceed renal reabsorption capacity. However, the local concentrations of calcium in the bone remain elevated, and urinary calcium wasting is not a major contributor to bone loss.

(Choice C) Supraphysiologic glucocorticoid (eg, prednisone) doses can cause osteoporosis, in part due to decreased proliferation and differentiation of osteoblast precursor cells. PTH increases the differentiation of osteoblast precursors; osteoporosis occurs in hyperparathyroidism because of a proportionally greater increase in osteoclast activity.

Educational objective:
Parathyroid hormone directly stimulates osteoblasts, leading to increased bone formation. Expression of RANK-L on osteoblasts induces increased bone resorption via a paracrine effect on nearby osteoclasts. Hyperparathyroidism causes increased RANK-L expression and decreased expression of osteoprotegerin, leading to net bone loss.

Pathophysiology Endocrine, Diabetes & Metabolism Hyperparathyroidism

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A 58-year-old man is seen in the clinic 6 months after undergoing right coronary artery stent placement due to unstable angina. His father died at age 50 from coronary artery disease. The patient follows a healthy diet and exercise plan and is compliant with his current medication regimen. BMI is 29 kg/m^2. Physical examination is unremarkable. After extensive discussion with the patient, evolocumab is added to his treatment plan. Which of the following is expected as an immediate result of this treatment?

A. Decreased hepatocyte cholesterol synthesis
B. Decreased intestinal cholesterol absorption
C. Decreased low-density lipoprotein receptor lysosomal degradation
D. Stimulation of lipoprotein lipase transcription
E. Stimulation of low-density lipoprotein receptor transcription

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A. ~~Decreased hepatocyte cholesterol synthesis~~ (3%)

B. ~~Decreased intestinal cholesterol absorption~~ (8%)

✓ C. Decreased low-density lipoprotein receptor lysosomal degradation (70%)

D. Stimulation of lipoprotein lipase transcription (5%)

✗ E. Stimulation of low-density lipoprotein receptor transcription (12%)

Incorrect
Correct answer
C

70%
Answered correctly

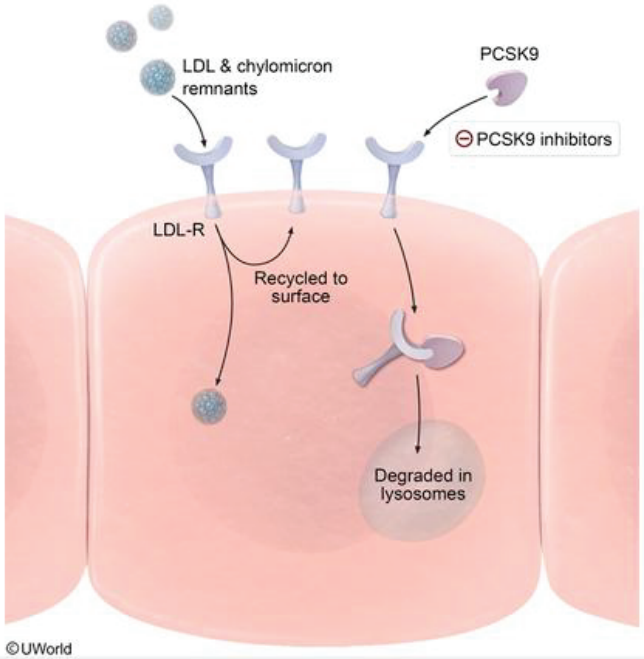
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PCSK9 inhibitor mechanism of action



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Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that regulates the concentration of **low-density lipoprotein receptor** (LDL-R) on the hepatocyte cell surface. Binding of PCSK9 to LDL-R causes increased lysosomal degradation of LDL-R, which leads to decreased uptake of circulating LDL into hepatocytes.

PCSK9 inhibitors (eg, evolocumab, alirocumab) are monoclonal antibodies that inhibit binding of PCSK9 to LDL-R, which **decreases LDL-R degradation** and increases the concentration of LDL-R remaining on the cell surface. This results in **greater uptake of LDL in the liver** and lower circulating LDL levels.

When statins are used to treat high LDL levels, circulating levels of PCSK9 are upregulated, suggesting that PCSK9 pathway inhibition may complement the LDL–lowering effect of statins. Therefore, PCSK9 inhibitors are indicated for high-risk patients who have **persistently elevated LDL** despite statin therapy; PCSK9 inhibitors reduce the risk of cardiovascular events (eg, myocardial infarction, stroke) in these patients.

(Choice A) Statins (eg, atorvastatin) are the primary, first-line lipid-lowering agents for patients who have atherosclerotic cardiovascular disease or are at increased atherosclerotic risk. They decrease hepatic cholesterol synthesis by inhibiting HMG-CoA reductase.

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cholesterol synthesis by inhibiting HMG-CoA reductase.

(Choice B) Ezetimibe is a lipid-lowering drug that directly inhibits absorption of cholesterol in the small intestine. PCSK9 inhibitors do not inhibit intestinal cholesterol absorption.

(Choice D) Insulin upregulates lipoprotein lipase, which hydrolyzes triglycerides in chylomicrons and VLDL; the liberated fatty acids are taken up in adipose tissue, leading to reduced plasma triglyceride levels. In contrast, PCSK9 inhibitors have little effect on triglycerides.

(Choice E) Thyroid hormone increases expression of LDL-R, as does estrogen and various dietary factors (eg, low saturated fat diet). However, the increase in cell-surface LDL-R from PCSK9 inhibitors is due to decreased lysosomal degradation, not increased transcription (synthesis).

Educational objective:

Binding of proprotein convertase subtilisin kexin 9 (PCSK9) to low-density lipoprotein receptor (LDL-R) on the hepatocyte cell surface increases degradation of LDL-R, leading to decreased uptake of circulating LDL. PCSK9 inhibitors (eg, evolocumab, alirocumab) decrease LDL-R degradation, resulting in greater uptake of LDL in the liver and lower circulating LDL levels.

References

- PCSK9 inhibitors: clinical evidence and implementation.

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